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Original Articles

STUDIES ON THE RELATION OF THE ADRENAL GLANDS TO ALLERGIC PHENOMENA

I. THE OUTPUT OF EPINEPHRINE DURING ANAPHYLACTIC SHOCK IN DOGS*†

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THE well-known effects of epinephrine in human allergic manifestations suggest a possible rôle of the adrenal gland in such conditions. It is conceivable that, in certain cases, an absorbed dose of allergen might lead to reactions which influence the epinephrine output from the adrenal medulla. Thus, the periodicity of allergic attacks may be related to such changes in the rate of liberation of epinephrine from the adrenal glands. If an increase in epinephrine output is present, it could probably react favorably, while a diminution might be unfavorable.

It has been demonstrated by Stewart and Rogoff (1919) that the epinephrine output of the adrenal glands can be increased, in experimental animals, by nerve or drug stimulation. For example, a dose of strychnine sufficient to augment reflex activity in anesthetized dogs or cats will stimulate the adrenal medulla through its nervous mechanism so that up to about 30 multiples of the ordinary output of epinephrine will be produced and liberated into the circulation. This increase in output lasts for a number of hours and occurs in all animals studied. If an increase of the same magnitude could be elicited in man, the amounts so liberated would be equivalent to about 1 c.c. of 1:1,000 adrenalin per hour, delivered at a fairly uniform rate. Such an amount is much greater than that ordinarily needed, at periodic intervals, to control allergic symptoms in most patients. From the amounts of strychnine which yielded these results in anesthetized animals it has

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been calculated that for an adult human being the corresponding dose would be about 5 to 10 mg. (gr. 1/12 to gr. 1/6) of strychnine sulphate. These amounts are less than the convulsive dose but would produce marked hypertonicity in the absence of anesthesia or sedative drugs.

If a therapeutic dose of strychnine leads to increased liberation of epinephrine in allergic persons, in the same manner as in experimental animals, it is possible that strychnine might be useful as a means of furnishing the patient with the equivalent of a prolonged administration of epinephrine in amounts sufficient to control some distressing allergic symptoms. Preliminary observations on the use of strychnine in human allergy have been made at the Asthma and Hay Fever Clinic. Our results are reserved for publication after more extensive investigation.

In addition to the information already available as a basis for administration of strychnine to patients with allergic symptoms, the following questions presented themselves for investigation: (1) Since there is experimental proof that subcutaneous administration of epinephrine causes different physiologic responses from intravenous administration of the same amount, it is desirable to determine whether the therapeutic effects of the drug differ in the same manner. (2) If strychnine augments the epinephrine output in man as in experimental animals, to what extent can this influence clinical conditions? (3) Is the epinephrine output of the adrenal medulla altered during anaphylactic shock?

The present article is concerned with the last of these questions. There are a number of reports, in the literature, of investigations on the relation of the adrenal glands to anaphylaxis.

The histologic appearance of the adrenal glands in anaphylaxis was investigated by Olbrycht and Ramult (1923). In death from anaphylactic shock no change was found in the adrenals of guinea pigs and rabbits, although in prolonged shocks there were some changes, according to the length of survival of the animals. In dogs, they did not succeed in inducing fatal shock. The animals recovered in from two to three hours after the shock injection, and the changes in the adrenals consisted of slight hyperemia of the medulla with an insignificant decrease in the chromaffin substance.

Flashman (1926) concluded that there is marked increase in susceptibility to anaphylactic shock, produced by intraperitoneal injections of horse serum, in adrenalectomized rats, regardless of whether the animals are sensitized before or after extirpation of the adrenals, and that this seems related chiefly to the degree of insufficiency. His experiments consisted of one group of 4 rats, sensitized after and one group of 5 rats sensitized before ablation of the adrenals. Six control rats were used.

Wyman (1929) observed increased susceptibility to anaphylactic shock in adrenalectomized rats and concluded that the increase in sus-

ceptibility is not related to cortical insufficiency but is consequent to the lack of medullary adrenal tissue. He also obtained some evidence suggesting a probable protective influence of injections of epinephrine. Such an influence of epinephrine, in guinea pigs, was observed by Hanzlik and Karsner (1920) and by Hájos (1926).

In guinea pigs, subjected to removal of one adrenal and a large part of the opposite gland, increased sensitivity to active anaphylaxis but not to passive was reported by Kepinow (1922). However, from a study on more than 100 guinea pigs, Karsner and Ecker (1924) state, "Experimental anaphylactic shock produced in sensitized guinea pigs by intravenous injection of homologous serum permits no satisfactory interpretation of relative degrees of sensitization or inhibition, either on the basis of clinical symptoms or fatal results."

Although rats are not generally recognized as suitable animals for studies in anaphylaxis, we may assume that any differences in susceptibility between normal and adrenalectomized, in the small numbers of animals used in the above mentioned reports, could not be relied upon as indicating more than a relation of the medulla, if anything, to the observed phenomena. The frequent occurrence of accessory cortical bodies renders the rat unreliable for studies in cortical insufficiency on adrenalectomized animals. In the experiments upon guinea pigs, in which one adrenal and a major portion of the opposite gland are excised, only a relation of lack of epinephrine from the medulla could be properly considered.

Smith and Ravitz (1920) found no effect upon the epinephrine content of the adrenals, in anaphylactic shock, in guinea pigs and rabbits. The same results were obtained in guinea pigs by Mouriquand, Leulier and Sédallion (1929).

The epinephrine output of the adrenals in anaphylactic shock was examined by Houssay and Molinelli (1926) and by Tournade and Hermann (1927). These investigators reported an increase in the rate of epinephrine secretion. In both cases the method employed was that of Tournade and Chabrot, which consists of uniting an adrenal vein of one dog with the jugular vein of another and recording changes in blood pressure and heart rate in the recipient. The other adrenal of the donor is extirpated, and in the recipient the vagi are sectioned and the stellate ganglia excised. Since the conclusion reached by the above mentioned investigators is not in harmony with the results of our studies, it is necessary to discuss briefly their method and results as well as our own. Indeed, we believe critical analyses of methods in endocrine researches are especially valuable, since there seems to be a growing tendency to apply prematurely, in clinical practice of medicine and surgery, some results or speculations based upon experimental investigations. Such practices are to be deprecated as endangering human lives.

The method of Tournade and Chabrot is not free from certain serious

objections, some of which have already been raised by Hallion. The donor is usually two or more times as large as the recipient, and blood is constantly passing from the larger to the smaller animal. In an experiment, like that reported by Houssay and Molinelli, in which transfusion continues for at least twenty minutes, a considerable volume of blood may be added to the circulation in the recipient. This may equal about one-third to one-half of the total blood volume of the recipient if the ordinary blood flow through the adrenal of the donor remains unaltered. The recipient is not adrenalectomized; in addition to the epinephrine secreted by his own adrenals he receives that of one adrenal of a much larger dog over the period of the transfusion. These factors can play a part in the blood pressure or heart rate changes that may occur in the test animal. The rate of epinephrine secretion from the donor's adrenal cannot be quantitatively ascertained, nor can the rate of blood flow.

It is significant that when anaphylactic shock was induced in the donor and the blood pressure fell, a reaction was not obtained in the recipient until the blood pressure in the donor was returning to normal, thus reestablishing an adequate blood flow from the larger to the smaller dog. It may be pointed out, also, that if epinephrine is secreted normally during the period of retarded circulation in the donor, it would accumulate in the capillaries and veins of the adrenal, to be "washed out" in relatively greater concentration in the transfused blood when the rising pressure permits an increased blood flow through the gland. A reaction might thus be obtained in the recipient which is truly an epinephrine reaction, yet does not represent an increase in the rate of secretion by the gland. In our opinion, the procedure adopted by Dreyer (1899) and by Tscheboksaroff (1910), consisting of collecting blood from the adrenals of one dog and injecting it into the circulation of a smaller dog, to observe the effects upon blood pressure, is much less objectionable than the method under discussion.

Finally, it is conceivable that anaphylactic shock might suppress epinephrine secretion from the adrenal and that the reaction observed might be caused by another substance carried in the blood of the donor to the test animal. Thus, since the reaction relied upon is a rise in blood pressure and acceleration of the denervated heart in the recipient, may it not be suggested, in the light of Cannon's recent publications, that these effects when obtained might be produced by the passage of "sympathin" in the blood of the donor to the reacting animal?

It is difficult to interpret the statement made by Houssay and Molinelli concerning the influence of anaphylaxis. They state, "Its effects corresponded with those of an injection of 0.005 mg. epinephrine, but they were generally prolonged; four minutes in two cases and twenty minutes in another." This does not indicate whether there was in every case a liberation of 0.005 mg. epinephrine (over a period of

four minutes in 2 cases and twenty minutes in the third) or an increase in that amount over the same period. If this is intended to represent an *increase* in output, the question must be asked "what was the *initial* rate of secretion, before anaphylactic shock?" The method, as employed, cannot yield quantitative information on the rate of liberation of epinephrine from the adrenal before and after induction of anaphylaxis. It can, at most, be relied upon as a nonspecific, qualitative procedure. These criticisms are made without the least desire to reflect upon the excellence of the above mentioned work but only with the desire to determine the relative merits of different methods employed in the study of the problem under consideration.

The method employed by us for determining the epinephrine output of the adrenals, before and after inducing anaphylactic shock, is that of Stewart and Rogoff. While this method has certain limitations (apparently not recognized by some investigators who have attempted to employ it), it is correct in principle, since measurement of the rate at which epinephrine is given off from the adrenals under any given conditions necessarily involves the measurement of a mass (epinephrine concentration in adrenal vein blood) and a time (blood flow through the gland)—the mathematical conditions which govern the measurement of every velocity. The method is sufficiently sensitive to permit reliable determinations of the epinephrine output under ordinary experimental conditions as well as changes in output, in either direction, under special conditions. Notwithstanding any objections that might be suggested, it is at present the most satisfactory quantitative method for studies on the rate of liberation of epinephrine from the adrenal glands. With adequate experience and when properly employed it yields consistent results which, if correctly interpreted, are within the ordinary limits of error of a physiologic method.

Our experiments were performed on dogs. Nine animals were sensitized with horse serum, 5 c.c. on two or three successive or alternate days. The first dose was administered subcutaneously in all cases, the subsequent doses intravenously in some and subcutaneously in others. The shock experiments and determinations of epinephrine output were performed four to five weeks after administration of the sensitizing serum. In two animals intravenous injection of 5 c.c. of horse serum failed to produce shock; in all the others definite shock was obtained varying in intensity. The maximum fall in blood pressure observed was 90 mm. Hg, the minimum 24 mm. The maximum initial pressure, before shock, was 140 mm., the minimum 74 mm. The maximum pressure observed during shock was 50 mm., the minimum 16 mm. The other characteristic phenomena (especially intestinal) of anaphylaxis in dogs were observed in all the animals, varying in degree with the intensity of the shock. Clotting of blood was very much delayed in the shocked animals.

In one dog (No. 6) there was no evidence whatever of any effect produced by administration of the shock dose of horse serum. In another (No. 1) the injection of serum did not cause visible phenomena of shock. However, the blood flow from the adrenals was reduced to about one-third and the red blood cell count increased from 7,100,000 to 9,560,000. It is possible, therefore, that there was a moderate anaphylactic reaction which did not manifest itself in a profound change in blood pressure. The pressure, already low (60 mm.), only fell to 50 mm. Hg. Whether or not the observed phenomena are interpreted as an anaphylactic reaction, there was no change in the epinephrine output from the adrenals. Dog 7 was pregnant and the uterus, with the fetuses, was removed before the collection of Specimen 1.

The blood pressures, in millimeters of mercury, before introduction of the shock dose of serum in Dogs 1 to 9, respectively, were as follows: 60, 74, 74, 114, 140, 96, 78, 80, 110. The rates of epinephrine output in milligrams per kilogram of body weight, per minute were, 0.0002, 0.00025, 0.00029, 0.00018, 0.00043 (Dog 6, not assayed), 0.00015, 0.00049, and 0.00026.

After administration of the shock dose of serum, the blood pressures were, 50, 50, 28, 30, 48 at onset of shock and 46 later, 100, 20, 16, 32 at onset of shock and 20 later. The corresponding epinephrine outputs were, 0.0002, 0.00032, 0.00082, 0.00028, 0.00039 at onset of shock and 0.0003 later (Dog 6, not assayed), 0.00017, 0.00048, 0.0008 at onset of shock and 0.00054 later.

For convenience, these results, together with a number of details of the epinephrine assays and other information, have been assembled in tabular form for publication in the *American Journal of Physiology* (1933), to which the reader is referred. No essential differences in the rates of epinephrine secretion, before and after induction of shock, occurred in any of the experiments.

One condensed protocol will suffice to furnish details not included in the table. For this purpose we have selected one of the two experiments (Nos. 3 and 9) in which the calculated output of epinephrine might indicate a moderate apparent increase during anaphylactic shock. In our opinion, these figures should not be interpreted as a significant increase in the rate of epinephrine output.

With the very slow blood flow, the epinephrine concentration in the adrenal blood was so great that dilution of the specimens with indifferent blood and then with Ringer's solution was found necessary in order to obtain satisfactory reactions upon intestine segments, to permit quantitative interpretations. This, of course, introduces or magnifies factors of possible error in the final calculation of the rate of epinephrine secretion. For this reason the figures, in this case, cannot be relied upon as indicating an increase in epinephrine output.

Even if these figures were obtained with specimens collected with larger blood flows and of much lower epinephrine concentrations, it would require a considerable number of confirmatory experiments to warrant the interpretation of an augmented rate of epinephrine secretion, since the figures are not above the upper limits of the normal range obtained by this method in the large series of experiments by Stewart and Rogoff (1917, 1919, 1923).

CONDENSED PROTOCOL. DOG 9, FEMALE, WEIGHT 5.0 KG.

Dec. 3, 1932. Subcutaneous injection of 5 c.c. horse serum.

Dec. 5, 1932. Intravenous injection of 5 c.c. horse serum.

Dec. 31, 1932. Under ether anesthesia, prepared cava pocket, inserted cannulas for blood pressure and for collection of blood specimens. 10:10 A.M., adrenal blood specimen (1) obtained, 7.6 gm. in 90 seconds = 5.1 gm. per minute. Blood pressure, 110 mm. Hg. 10:18 A.M., intravenous injection of 3 c.c. horse serum.

As the blood pressure fell rapidly, the respiratory rate diminished. 10:21 A.M., adrenal blood specimen (2) obtained, 3.1 gm. in four minutes = 0.8 gm. per minute. Blood pressure, 32 mm. Hg. 11:00 A.M., adrenal blood specimen (3) obtained, 2.3 gm. in four minutes = 0.6 gm. per minute. Blood pressure, 20 mm. Hg.

Indifferent blood was obtained before and after the intravenous injection of serum. Clotting was very markedly delayed in all the blood specimens obtained after shock was induced. Violent peristaltic rushes occurred repeatedly throughout the experiment.

The first adrenal blood specimen, collected before induction of shock, was decidedly stronger than 1:6,000,000, weaker than 1:3,000,000 and somewhat stronger than 1:4,500,000 adrenalin. It was assayed as 1:4,000,000, corresponding to an output of 0.0013 mg. per minute for the dog or 0.00026 per minute per kg. of body weight.

The second adrenal blood specimen, collected three minutes after intravenous injection of horse serum and just as shock phenomena developed, was too strong to permit assay with a rabbit's intestine segment without previous dilution. It was found necessary to dilute it with 3 volumes of indifferent blood and then with 3 volumes of Ringer's solution. In this manner it was determined that the concentration of epinephrine in the blood was somewhere between 1:175,000 and 1:225,000, and it was assayed as 1:200,000 adrenalin, corresponding to an output of 0.004 mg. per minute for the dog or 0.0008 mg. per minute per kg. of body weight.

The third adrenal blood specimen, collected forty minutes after the shock injection of serum, also required dilution with indifferent blood as well as with Ringer's solution, before satisfactory reactions could be obtained with the intestine segment. It was found that this specimen

was stronger than 1:250,000 and weaker than 1:200,000. It was assayed as 1:225,000 adrenalin, corresponding to an output of 0.0027 mg. per minute for the dog or 0.00054 mg. per minute per kg. of body weight.

Comparing the epinephrine concentrations in the blood specimens obtained before and after shock could lead to the erroneous conclusion that the very much greater concentrations in Specimens 2 and 3 (after shock) demonstrate a large increase in epinephrine output. Examination of the above mentioned table, however, illustrates, what has been repeatedly emphasized by Stewart and Rogoff, that increase in epinephrine concentration, when not associated with increased output, is associated with a corresponding decrease in the rate of blood flow through the adrenals. A change in epinephrine output can be definitely determined only when there is a significant alteration in this relation between blood flow and epinephrine concentration. Thus, it is again emphasized that a method for quantitative determinations of changes in epinephrine output must permit measurement of the rate of blood flow from the adrenals as well as the epinephrine concentration in the blood.

It is not surprising that relatively high epinephrine concentrations were found in the adrenal blood specimens obtained in shocked animals, since the blood flows were decidedly reduced, in some cases to less than one-tenth of the initial rate before shock. As already mentioned, under these conditions blood "washed out" of the adrenal, as circulation through the gland improves, would carry epinephrine in greater concentration than normal in the adrenal blood, to a transfused animal and may cause reactions which cannot be properly interpreted as due to increased epinephrine output.

Our experiments include some in which the blood flow through the adrenals was very slow and others in which there was a very good flow. Adrenal blood specimens were obtained as soon as shock developed and at intervals ranging up to forty minutes after the onset of shock. In two experiments, one specimen was obtained at once and another later. Various degrees of intensity of anaphylactic shock were observed in the different animals. Nevertheless, there were no significant alterations in the rate of output of epinephrine from the adrenals which could be attributed to an influence of anaphylaxis upon the glands.

CONCLUSIONS

Anaphylactic shock, in dogs sensitized with horse serum, does not cause any significant alteration in the rate of epinephrine secretion from the adrenal glands.

In studies on the rate of secretion of epinephrine from the adrenal glands the method must permit quantitative observations upon the rate of blood flow through the glands as well as upon the epinephrine concentration in the adrenal blood.

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INTRAVENOUS POLLEN THERAPY*†

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THE following studies were undertaken to determine the effect of intravenous injection of pollen extracts. Because of the supposed extreme danger the first injection was given to a moribund patient. Since then a series of treatments has been given to five other patients, and the results are deemed sufficiently interesting to warrant a report.

EXPERIMENTAL

The extract used was made of short ragweed alone, washed with ether. The 3 per cent extract made with Coca's alkaline fluid contained 0.4 mg. per cubic centimeter of nitrogen. Dilutions for testing and treatment were made and kept on ice when not in use. The same batches of testing dilutions were used throughout the work to avoid possible differences in making up new supplies. The original extract was used for treatment throughout, and fresh dilutions were made as needed.

Testing was performed by scratch method with four dilutions (1:100, 1:250, 1:500, and 1:1,000) in addition to the whole pollen scratch test, and the transverse diameters of the wheals were recorded. Tests were repeated every week or two weeks with special care to avoid, as far as possible, variations in technic.

Ten patients (white) were available for treatment who had moderate or severe fall hay fever and medium or large scratch test reactions. Six patients, all male, received intravenous treatments; the other four were used as controls and given the usual subcutaneous treatments with the same extract. The first of the intravenous group was a patient in moribund condition with tuberculosis. In a previous communication[1] I have discussed the relations of coincidental pollinosis and tuberculosis. The protocols show the details of treatment and results of testing.

Technic.—Three dilutions (1:100, 1:1,000, and 1:10,000) were used. The number of units wanted for a treatment were measured out in a tuberculin syringe and injected into about 15 c.c. of sterile normal saline solution in a medicine glass. This was aspirated with a 20 c.c. syringe, the needle then attached and the syringe filled to the 20 c.c. mark from another medicine glass of normal saline. (This maneuver is to prevent the local reaction about the needle puncture.) The solution was then injected intravenously very slowly. Aseptic precautions and materials suitable for intravenous injections must of course, be

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used throughout. It is best to use a fairly large needle. Infiltration of the solution about the vein causes swelling and urticaria about the injection, and may make it impossible to finish the injection. After a number of treatments have been given, however, the amount of local reaction elicited by the solution becomes very slight.

In a few instances the dose was made up to 1, 5 or 10 c.c. This was discontinued because of the tendency for reactions to occur. Gravity method injection was used twice. This probably represents the ideal method of giving a pollen solution intravenously, since adequate dilution and slow drip render reactions less probable and less severe. Furthermore, it is possible to stop at any time that premonitory signs of a general reaction appear. The method is more cumbersome and time consuming, however.

Dosage.—Doses varied from 10 units to 2,000 units per treatment. The rate of increase is obviously a matter of judgment. It was found that there seemed to be a level of dosage which was difficult to pass, but after a repetition, the dose could again be increased without trouble.

Injections were given at various intervals from twice a week to once in two weeks.

One patient received only one intravenous injection. The highest number given was fifteen.

Reactions.—As stated above, the local reaction about the needle puncture and about the vein was troublesome at first, but later practically disappeared. Toward the end of the series of treatments, extravasation of the solution into the tissues caused no more reaction than normal saline solution. General reactions seen, consisted of several types, which are described in the order of frequency.

A. *Erythema Reaction.*—This comes on in one to ten minutes, depending upon the dose and dilution. A premonitory itching of the palms frequently precedes this, as also the other general reactions. The face, neck, chest and arms flush and become deep red in color, with subjective symptoms of heat and tenseness of the skin. If the reaction becomes more severe, blanched areas with a livid hue appear in plaques on the face, and the skin feels indurated and thick. The patients are not alarmed nor rendered unduly uncomfortable by this type of reaction. They are inclined to consider the peculiar appearance of the face a joke. The duration is usually from a few minutes to a half hour.

B. *Urticaria Reaction.*—Generalized urticaria, more marked over the upper part of the body, may appear in about ten minutes. It is frequently more marked on the arm where the injection is given. The site of the tourniquet may stand out as one large wheal all around the arm, traversed by fine red lines, where the skin was folded.

C. *Hay-Fever-Like Reaction.*—In a few minutes the patient begins to sneeze, watery discharge from the nose and eyes appears, and the

eyes and face become red. The sneezing may be very severe, and the attack may last twenty minutes, requiring adrenalin for relief.

D. *Focal Reaction.*—Urticaria confined to the sites of previous subcutaneous injections or scratch tests may occur.

E. *Asthma.*—A mild sense of constriction in the chest, accompanied by musical râles, appeared twice in one patient, and an attack of asthma lasting thirty minutes occurred in another.

F. *Collapse Reaction.*—A severe reaction occurred in the moribund patient who was given the first intravenous injection. Extreme anxiety, restlessness, feeble and rapid pulse but none of the above described usual manifestations of atopy occurred. This reaction seems to be related to extreme overdosage intravenously.

RESULTS

Result of Skin Tests.—Marked diminution in the size of skin reactions occurred in five patients. This was more evident than is obvious from the recorded diameters. Wheals which were large and raised, with much surrounding erythema, after a number of treatments, became small, very flat and had very slight erythema. In three patients, the scratch reaction to whole pollen decreased from a large wheal to a negative reaction or a slight erythema. The 1:100 dilution gave slightly larger reactions than the dry pollen. The latter was used mainly because it is not subject to deterioration. However, tests on the control patients gave results closely alike before and after treatment in three cases so that deterioration of the solutions was negligible. One of the control patients showed a moderate decrease in skin sensitivity.

Tests with giant ragweed and burweed marsh elder (whole dry pollen) also showed great decrease in size, but quantitative tests with dilutions were not done. In three of the intravenous cases sensitivity returned to normal in four to six weeks.

Passive Transfers.—Blood was drawn from all patients except Case 1 on Sept. 12 for passive transfer and precipitin tests. Passive transfer was made with 0.05 c.c. of serum to a number of normal subjects and tested with 0.02 c.c. of 1:100 pollen extract. All nine serums gave very good passive transfers with minor differences. In a number of instances the patients who received intravenous treatment had more active serums than the control cases. No comparison was made with serums taken before treatment. There is no doubt, however, that there is a plentiful supply of reagin in the blood of the patients who received intravenous treatment.

Precipitin Tests.—Serum was overlaid with 1:200 dilution of pollen extract and observed for twenty-four hours. No evidence of precipitins was seen in any of the nine serums.

Effect on Hay Fever.—The intravenous treatment was far more ef-

fective than the subcutaneous treatment, as seen in the control cases and in the regular patients (about 75) treated during this season at the Allergy Clinic of Rush Medical College.

The moribund patient died before the onset of the hay fever season. Blowing dry ragweed pollen into one nostril had caused no discomfort, sneezing or discharge.

The three patients whose treatments were started the earliest had the best results. Two had practically no symptoms, a slight nasal discharge and a rare sneeze on the worst mornings. The third had mild sneezing and discharge on several of the high pollen count days.

The last two patients began so late that the treatment may be considered coseasonal. Both had moderate to severe hay fever with asthma during the latter part of August. During the first week in September, when the pollen counts were at their highest, one patient was completely free of symptoms, the other markedly better, with no asthma.

The four control patients, treated with the same extract subcutaneously received from 28 to 33 injections each. Top dose: 1 patient, 800 units; 3 patients, 5,500 units. All stated they had more relief than during the previous season, but mild to moderate attacks of sneezing and discharge occurred on a considerable number of mornings. One patient had two attacks of asthma, requiring adrenalin on two damp nights. The previous season, with no treatment she had more or less wheezing continuously for three to four weeks.

In giving the intravenous treatments psychic effect was avoided as far as possible. The patients were not informed that there was anything new or unusual about such treatment.

DISCUSSION

The mechanism of the subcutaneous treatment of hay fever involves the following considerations: The atopen reacts with reagin in the skin and subcutaneous tissues with liberation of the H-substance and formation of wheal and flare. The atopen is fixed locally, but subsequently is probably removed by the blood, denaturized or broken down and eliminated. When removed from the point of injection, is it in combination with reagin, or alone? How soon is it removed? In the course of removal does it react further in the respiratory mucous membrane? Does the H-substance liberated by the local reaction affect the distant shock-tissues? How is the tolerance of the respiratory mucous membrane raised? Answers to all these questions are indefinite.

In the administration of most drugs, subcutaneous treatment is the same as intravenous with the exception of speed of action. In the special case of an atopen, however, the fact that a local reaction occurs in the subcutaneous method changes the picture. If the atopen were merely delayed in absorption, this would be an ideal method of treat-

ment. We do not know accurately what occurs as a sequence to the local reaction. Perhaps the atopen is changed so that it is not absorbed as such. Perhaps rates of absorption vary at different times and in different individuals between wide limits. Thus the subcutaneous method introduces a series of unknowns with the local reaction so that we do not know whether we are actually treating the respiratory mucous membrane with the atopen itself or with one of its products, and to what extent differences in denaturization and absorption rates affect our therapy.

There can be no doubt, however, that the mechanism of increase in tolerance must involve the reaction of the atopen or one of its products on the respiratory mucous membrane after each injection. If this is true it becomes a rational procedure to treat the site of trouble directly via the blood stream, rather than through the intervention of another shock tissue. The respiratory mucous membrane, in fact all sensitive tissues, are treated directly by a series of exposures to gradually increasing concentrations of atopen. Fixation of atopen is distributed throughout a large area so that reaction at any one point is minimal, instead of being concentrated in one area with swelling, redness and urticaria.

The reactions evolved by intravenous administration are shock-tissue reactions with the possible exception of the collapse reaction. Apparently no reaction occurs in the blood stream ordinarily. This agrees well with previous theories. According to Foran and Lichtenstein[2] atopen and reagin probably do not react in the absence of the shock-tissues; according to Walzer[3] reagin is neutralized, but it may require a number of hours. Harley[4] states that reagin and atopen do not react in the blood stream. In any event, the work outlined here indicates that the shock-tissues pick up and fix the atopen quickly without any evidence of a reaction in the blood stream as a rule. The collapse reaction may possibly be due to a reaction in the blood, but may perhaps be evidence of a reaction in an unusual shock organ, such as the liver.

The depression of skin sensitivity in these patients, while the serum still contained a large quantity of reagin, indicates that the skin does not become readily resaturated with reagin under the conditions outlined. The reason which suggests itself for this phenomenon is that the fixation of atopen throughout the skin in some way prevents the union of reagin with cells. With intravenous treatment the atopen is distributed throughout the skin surface. With subcutaneous therapy, the bulk of the atopen is fixed in situ, and probably only a fraction escapes in a form suitable for fixation elsewhere, so that the depression of skin sensitivity is relatively small. Thus in each control case, the total amount of pollen given was at least ten times the amount given each of the intravenous patients, yet the depression of sensitivity was

much greater in the latter group. This proves that the actual amount of free atopen finding its way into the blood stream in the subcutaneous group was less than in the other, and therefore a very small fraction of the total dose administered.

With the above mentioned facts in mind, we may formulate the following hypothesis to explain the mechanism of tolerance: Atopen circulating in the blood is taken up and fixed by the shock-tissues. The period during which the atopen remains fixed is probably considerable, ranging from a few hours to several weeks. During this period the shock-tissue is inhibited from resaturating itself with reagin from the blood stream, and thus there is a reduced supply of free reagin available in the shock-tissues capable of reacting with more atopen. In other words this hypothesis postulates that the fixation of atopen is accompanied by a binding of reagin and that more reagin is not taken up until the combination is removed, which may require a considerable length of time. During this period, sensitivity is depressed because of the lowered supply of free reagin in the tissue. The reason for the lack of establishment of any marked degree of tolerance by the inhalation of pollen may be the failure of fixation of atopen because of lack of penetration into the tissue (or possibly because it is washed away by secretions).

In analyzing the concept of tolerance, the question arises whether tolerance consists in failure to react with the atopen or in a reduced intensity of reaction to the liberated H-substance. If the above hypothesis is correct, it would point to the former explanation.

Skin Sensitivity.—The depression of sensitivity seen in these studies was too marked to allow of any misinterpretation, although there have been marked differences of opinion concerning this phase in subcutaneous therapy.[5]

Too much stress, however, should not be placed on the findings in Case 1 because of his moribund condition. The skin reaction in this patient practically disappeared following a severe constitutional reaction, and returned later. (In this respect it is of interest to note that in three patients who died of tuberculosis, no definite decrease in the size of the scratch test with whole pollen was evident up to the time of death. This is in contrast to the marked decrease in skin sensitivity to tuberculin which usually occurs in moribund patients.)

Usefulness as a Method of Treatment.—The usefulness of any method of treatment depends upon its safety, effectiveness and practicability.

The safety of the intravenous method is the most important point involved, and of course can only be settled when sufficient trial of the method has taken place. The general fear of intravenous injection is based mainly on analogies with anaphylaxis and on the results of accidental intravenous injection in the course of subcutaneous treat-

ment. The actual number of fatalities recorded as due to pollen injections are far less than those due to horse serum.

A number of the reactions which occurred in this series were largely due to the rapid rate of increase in dosage used in some cases and could probably have been obviated. A slower rate of increase, as seen in Case 2, caused practically no reactions, and a high final dose was reached.

The most important causes of general reactions in the subcutaneous treatment are two: overdose and accidental intravenous injection. The latter is entirely obviated by the intravenous method. This method exposes the shock-tissues to gradually increasing concentrations which cause little reaction unless overdosage occurs. The danger of overdosage is present in both methods. The subcutaneous method has the advantage of the tourniquet. The intravenous method has the advantage of unlimited possibilities of dilution and slow rate of administration. Overdosage due to errors in measuring out the dose would be much more serious in the intravenous method.

The effectiveness of the intravenous versus the subcutaneous method can only be settled when a larger number of cases has been treated by the intravenous method. The results have been outstanding in the few cases tried here, in spite of the small number of injections given some of the patients and the late start in two cases. If the possibility of causing a definite decrease in skin sensitivity should prove to be a fact in a large percentage of cases, it would be a preseasonal guide to further therapy. The results seen in these patients have created the strong impression that ten intravenous treatments will give more relief than the usual twenty-five or thirty subcutaneous injections.

In practicability, the method has certain disadvantages. It cannot be used where intravenous injection is impossible or difficult, and it requires more time and care in giving each injection. With practice, the preparation and giving of the injections become relatively simple. A smaller number of injections per patient through the season compensates for the extra time spent on each injection.

The intravenous method must be considered an experiment to be used only by those who have had considerable experience in allergy.

CONCLUSIONS

1. Intravenous pollen therapy has been highly effective and not especially dangerous in a short series of patients.

2. Skin sensitivity was markedly depressed in five of the six patients and returned to normal after treatment was discontinued.

3. The blood contained a plentiful supply of reagin at the same time that skin sensitivity was depressed.

PROTOCOLS

The reactions following the various treatments are indicated by E for erythema; U for urticaria; A for asthma; and S for sneezing. The transverse diameters of the skin tests are recorded in centimeters. The recording of 0.1 cm. and 0.2 cm. may be considered negative or doubtful reactions, as they usually consisted mainly of the small papule due to trauma. The protocols concerning the control cases are not recorded here, as the important facts have been given in the discussion.

CASE 1.—Male, aged thirty-six years. Far advanced pulmonary and genitourinary tuberculosis with septic temperature. In moribund condition but little change had occurred for several months. Hay fever with very marked eye and nose symptoms, for two years. Subcutaneous treatment gave about 80 per cent relief in 1932. Scratch tests with whole pollen on May 3, 1933, gave wheal 1.5 cm. in diameter, erythema 4 cm. On May 5 an intravenous injection was given by gravity method with ragweed extract in a dilution of 1:20,000. It was intended to run the solution in very slowly, but by error about 15 c.c. (about 900 units) were injected within three or four minutes. The patient almost at once showed signs of restlessness, complained of peculiar and alarming sensations, had very rapid and feeble pulse and livid color. No asthma, hay fever or urticaria occurred. Prompt intravenous injection of 0.2 c.c. of adrenalin was given, followed shortly by 1 c.c. subcutaneously. The symptoms subsided in about thirty minutes, and the patient went to sleep in one hour. The next day he felt the same as usual. Scratch test on May 18 with whole pollen gave no wheal, erythema 1 cm. in diameter. On May 28 blowing ragweed into one nostril caused no symptoms. On May 28 two tests gave the same result. On July 8 two tests showed wheal 0.6 cm., erythema 3.5 cm. and on July 22 about the same. On August 1 the patient died of tuberculosis. A few hours later skin test gave no reaction.

CASE 2.—Male, aged forty-one years. Hay fever with asthma for four years. Last season had marked eye and nose symptoms and was

DATE 1933	UNITS I.V.	REACTION		DATE 1933	WHOLE POLLEN	SHORT RAGWEED SKIN TESTS 1:1,000	1:500	1:250	1:100
5/22	10			5/26	1.2				
5/24	20			6/14		0.2	0.5	0.5	0.7
5/26	30			7/ 5	0.5				0.2
5/29	100	E++		7/26	0.2	0.1	0.2	0.3	0.5
6/ 2	100			8/ 9	0.1	0.1	0.2	0.3	0.5
6/ 9	200	E+	U+	8/30	0.1	0.1	0.1	0.1	0.6
6/16	250			9/14	0.5			0.3	1.0
6/23	400			9/20	0.6		0.2	0.3	0.8
6/30	800			10/ 6	1.0	0.2	0.4	0.6	1.2
7/12	1,500			10/18	1.2	0.3	0.4	0.6	1.6
7/26	1,500								
8/ 9	2,000	E+							
8/23	2,000								
9/ 6	1,800								

unable to sleep many nights. Never had injection treatment before. This season symptoms were practically absent. He was unable to note any difference in symptoms on the highest pollen count day of the season.

CASE 3.—Male, aged twenty-three years. Hay fever four years with red eyes, violent sneezing and profuse watery discharge for six weeks each season. During 1932 had 17 subcutaneous injections, with but slight relief. During 1933 with 9 intravenous injections: no really bad day, slight discharge but hardly any sneezing and sleep was not disturbed. Because of the rapid increase in dosage, this patient had some reaction after most treatments.

DATE 1933	UNITS I.V.	REACTION	REACTION R FOR	DATE 1933	WHOLE POLLEN	SHORT RAGWEED SKIN TESTS 1:1,000	1:500	1:250	1:100
7/12	100			7/18	0.6	0.5	0.7	0.5	0.7
7/19	500	E++ U+	Adrenalin 0.5 c.c.	7/28	0.5	0.6	0.6	0.7	0.8
7/26	750	E++ U+	Adrenalin 0.9 c.c.	8/18	0.5	0.5	0.5	0.5	0.7
8/ 2	600	E(sl)		8/30	0.2	0.2	0.3	0.4	0.5
8/ 9	750	E+ A(sl)	Adrenalin 0.5 c.c.	9/14	0.2	0.1	0.3	0.4	0.4
8/16	800	E(sl)		9/20	0.5	0.1	0.4	0.6	0.6
8/23	1,000	E+		10/ 6	0.6	0.2	0.4	0.5	0.5
8/30	900	E(sl)		10/18	0.9	0.4	0.5	0.6	0.8
9/ 6	800	S(sl)							

CASE 4.—Male, aged thirty-four years. Hay fever for three years with marked eye and nose symptoms. In 1932 he received 26 subcutaneous treatments with considerable relief. In 1933 he received 9 intravenous injections: had four moderately bad days; result, far better than last year's.

DATE 1933	UNITS I.V.	REACTION	DATE 1933	WHOLE POLLEN	SHORT RAGWEED SKIN TESTS 1:1,000	1:500	1:250	1:100
7/12	100		7/24	1.0	0.3	0.3	0.3	1.0
7/19	300		8/18	0.1	0.1	0.2	0.3	0.8
7/26	600	E+	8/24		0.1	0.1	0.3	0.4
8/ 2	600	E(sl)	9/14	0.2				0.4
8/ 9	800	E(sl)	9/20	0.5			0.2	0.4
8/16	800		10/ 6	0.8	0.2	0.4	0.5	0.5
8/23	1,200	E+ S+	10/20	0.5	0.1	0.3	0.4	0.6
8/30	1,000	S(sl)						
9/ 6	1,000							

CASE 5.—Male, aged twenty-six years. Hay fever, spring and fall for thirteen years. Had never taken treatment. Sensitive to June grass, timothy, ragweed and wheat. In 1933 had spring hay fever very severely with asthma. Coseasonal subcutaneous therapy gave slight relief. Intravenous treatment was begun late and the patient had violent hay fever with asthma during the last half of August, although pollen counts were not at their height. During September the symp-

toms became much milder, and the patient had no asthma during the period of highest pollen counts.

DATE 1933	UNITS I.V.	REACTION	℞ FOR REACTION	DATE 1933	WHOLE POLLEN	SHORT RAGWEED SKIN TESTS 1:1,000	1:500	1:250	1:100
7/31	100	S++++	Adrenalin 0.8 c.c.	6/ 9	1.2				
8/ 7	20			8/30	0.8	0.4	0.5	0.8	1.5
8/11	40			9/11	0.4	0.2	0.5	0.8	1.5
8/14	30	S (sl)		10/18	0.6	0.3	0.4	0.6	0.6
8/18	60	S (sl)							
8/21	100	S+++	Adrenalin 0.5 c.c.						
8/25	100	S++							
9/ 1	100								
9/ 5	150								
9/ 8	200								
9/14	400								
9/25	500	S++							

CASE 6.—Male, aged thirty-six years. Hay fever three years with marked nose and eye symptoms and occasional attacks of asthma. Never had treatment before. Intravenous treatment begun August 9, 1933. Had severe hay fever with asthma on August 16, mild hay fever from August 21 to 25, slight asthma September 1 and 2, and thereafter had no symptoms at all for remainder of season.

DATE 1933	UNITS I.V.	REACTION	℞ FOR REACTION	DATE 1933	WHOLE POLLEN	SHORT RAGWEED SKIN TESTS 1:1,000	1:500	1:250	1:100
8/ 9	20			8/ 8	0.7	0.2	0.3	0.4	0.8
8/11	40			8/28	0.4	0.1	0.2	0.4	0.5
8/14	70	S (sl)		9/11	0.6	0.1	0.3	0.4	0.8
8/16	100		Adrenalin 0.6 c.c.	9/20	1.2	0.2	0.4	0.6	0.5
8/18	60								
8/21	70								
8/23	100	S (sl)							
8/25	100	S (sl)							
8/28	150								
9/ 1	150	A (sl)							
9/ 5	200								
9/ 8	250								
9/14	400	A+							
9/18	400								
9/27	300								

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THE RELATION OF PAPULAR URTICARIA AND PRURIGO MITIS TO ALLERGY*†

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DEFINITION OF "PAPULAR URTICARIA" AND "PRURIGO MITIS"

THE term "papular urticaria" was originally employed by Hebra in 1860, but the disease was first recognized, defined, and classified by Willan in 1798 under the name of "strophulus."‡ The earliest complete description of this malady, however, must be accredited to Bateman, Willan's associate, who, in 1814, gave a fairly accurate account of this ailment under the title of "lichen urticatus." This condition was discussed by subsequent writers under such varied names as "strophulus," "strophulus pruriginosus," "lichen simplex acute," "prurigo temperanea," "prurigo simplex," "prurigo simplex acute," "urticaria of infancy and childhood," and others.

From the time of Hebra, the German school of dermatology, almost as a unit, considered papular urticaria as a variety of urticaria. The French school, however, beginning with Bazin in 1860, was inclined to look upon this malady as a mild type of prurigo, and consequently grouped and discussed papular urticaria and prurigo together. The English dermatologists have been divided in their opinions on this question, while the Americans almost unanimously supported the German view. Within recent years, however, there has been a slow but general conversion toward a modified French conception of these diseases, and papular urticaria, under varying titles, is more and more being considered as the mildest type of the prurigos.

The word "prurigo" was employed by the oldest dermatologic writers synonymously with "pruritus." Willan first attempted to restrict the term to a definite type of a pruritic dermatosis, but in this he was only partly successful. In 1860, Hebra, however, definitely separated prurigo from a large heterogeneous group of pruritic dermatoses. He limited the term to the prurigo described by him, and now known as Hebra's prurigo, which is considered a chronic, incurable, pruriginous, papular dermatitis. Kaposi later described a milder and curable form of the disease, prurigo mitis; it is this latter type of the prurigos which is included in these studies.

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‡The history of the development of the conceptions of papular urticaria and prurigo will be presented by one of the authors in greater detail in another communication to be published shortly.

The Hebra and Kaposi prurigos, until very recently were the only varieties grouped under the head of "prurigo" by the majority of the German, English, and American dermatologists. The French, however, applied the term more broadly to a variety of diseases characterized by a primary pruritus most frequently of internal origin, and occurring in individuals predisposed to such illnesses because of a "dartre" or diathesis. It was their belief that the anatomic lesions which followed the pruritus in these diseases varied in different patients as a result of peculiarities inherent in the individual skins. The cutaneous manifestations in prurigo might, therefore, include erythemas, wheals, papules, vesicles, and other lesions, individually or in combinations, with or without lichenification or eczematization. Hence, according to the French, prurigo included papular urticaria, the prurigos of Hebra and Kaposi, the prurigo of Besnier, the neurodermites, and other localized and generalized pruritic dermatoses.

In most of the recent writings on these subjects, prurigo mitis and papular urticaria are grouped together, and discussed as manifestations based upon a common mechanism, although they are not necessarily attributed to the same etiologic factors. We have adopted this practice in the present communication and are presenting the results of our studies in both of these diseases, namely, papular urticaria and the prurigo mitis of Kaposi.

PAPULAR URTICARIA

The primary lesion of papular urticaria is an erythematous patch from one-quarter to one-half inch in diameter, irregular or oval in outline, on the level with the skin or slightly elevated, and surmounted by a central conical, usually follicular papule, the size of a millet seed, and of a deep red color. Occasionally a number of these erythematous patches fuse, and thus form a large patch with a number of papules surmounting it. On diascopic pressure, the ivory color of the wheal is demonstrable in the papular area.

The lesions are markedly pruritic. As a result of the trauma produced by the scratching, many excoriated, bleeding, and crusted papules may be seen. Occasionally infection follows producing papulopustules or pustules. The skin in the affected areas between the lesions, however, always remains smooth and soft, irrespective of the duration or the intensity of the disease.

Many cases show additional cutaneous changes. In some instances, tiny vesicles surmounting the papules may be noted. Frequently, the papule, as it recedes, becomes flattened, smooth, shiny, and lichenoid in appearance (hence, the name "lichen urticatus"). Occasionally the condition may be complicated by wheals of urticaria vulgaris or even by areas of angioneurotic edema.

The erythematous patch lasts from a few minutes to a few hours, but the duration of the papule is from a day to a week or more. On complete regression of the lesion, a faintly pigmented spot remains for a short time. Scarring as a result of the papular wheal does not usually occur.

The distribution of the rash is more or less characteristic. It is usually symmetrical, and affects the outer surfaces of the upper and lower extremities and buttocks. These areas are frequently the only ones involved. The face and trunk may show a few scattered lesions, and occasionally the trunk may present a rather profuse eruption.

The lesions occur in crops, which most frequently appear during the night. All stages in the development and regression of the papule may be noted at the same time. A single attack may last a week or two, but the illness may persist for months or years. There may be periods of seasonal remissions, which, when present, usually occur in the summer.

Papular urticaria may simulate other skin conditions, so that at certain periods of its development it may be confused with multiple insect bites, scabies, varicella, lichen planus, and prurigo mitis.

PRURIGO MITIS (KAPOSI)

Prurigo mitis begins during the first year of life, usually between the eighth and twelfth months, as a persistent papular urticaria which becomes progressively more aggravated. As the patient passes into the second year, the urticarial lesion is gradually replaced by the characteristic prurigo papule. Such papules at first are felt rather than seen, but soon become more elevated and remain so. They are hard, round or conical, millet seed in size, pale red or of normal skin color, with no surrounding areola. They may be few in number or profusely distributed, and are usually not grouped. The associated pruritus is most intense. As the disease progresses, new crops of papules continue to appear, and the urticarial element in the disease becomes less and less evident, until it is eventually absent entirely.

By the end of the second year or early in the third, the patient with prurigo mitis usually presents the following characteristics: The skin in the affected area is dark brown in color. The lesions are symmetrically distributed especially over the extensor surfaces of the extremities. They consist of isolated typical papules interspersed with many that are excoriated, bleeding, crusted, or pustular. Pea-sized scars, resulting from past papules, and varying in color from brown to white are intermingled with the papules. The eruption in the affected areas usually increases in profuseness from above downward, the forearms showing more lesions than the arms, and the legs more than the thighs. The flexor surfaces of the elbows and knees, the axillae, and the folds of the groins are not involved. The forehead very frequently shows

the lesions, while the chest, abdomen, buttocks, and sacral regions may be sparingly involved.

The skin in the affected areas is rough, dry, fissured, and thickened, with an exaggeration of the normal skin markings (lichenification). It is covered with a fine furfuraceous peeling. The entire process suggests a nutmeg-grater feeling to the touch. Weeping eczematous changes may also be noted in these areas. The external lymph glands are definitely enlarged and may remain so even after the eruption has temporarily subsided. Constitutional symptoms such as malnutrition, nervousness, and anemia eventually develop.

During the course of the disease, the patient may have periods of quiescence and of remissions. In this climate, the eruption frequently abates during the winter, only to recur with the onset of warmer weather. Prurigo mitis tends to disappear completely during late childhood or before the onset of puberty.

Prurigo mitis must be differentiated from papular urticaria, papular fungus diseases, neurodermite, Besnier's prurigo, ichthyosis, scabies, chronic urticaria, pediculosis, hydroa aestivale, and chronic pruritus from any internal cause (leucemia, Hodgkin's disease, etc.).

DIFFERENTIAL DIAGNOSIS BETWEEN PAPULAR URTICARIA AND PRURIGO MITIS

During the first year of the disease, a differential diagnosis between papular urticaria and prurigo mitis cannot be made, since both diseases have similar modes of onset. It is possible to distinguish these two diseases only when the characteristic prurigo papule becomes the dominant lesion. This stage is usually reached during the second or the early part of the third year of the illness. At this time, the patient with prurigo mitis shows a uniform type of lesions, the prurigo papules, in contrast to the wheals and their modifications, seen in papular urticaria. Scars, the remnants of past papules, are characteristic of prurigo and do not usually occur in papular urticaria, although tiny scars resulting from scratching and secondary infection are occasionally noted in the latter illness. The skin in the affected areas in prurigo mitis becomes hard, dry, rough, thickened (lichenification), and may even show eczematization, while in papular urticaria, irrespective of the duration of the disease, the skin between the lesions is soft, smooth, and moist. The distribution of the eruption on the extremities differs in each disease; in papular urticaria the lesions are evenly spread while in prurigo mitis, they are more numerous on the forearms than on the arms, and also more numerous on the legs than on the thighs. The enlarged lymph glands and constitutional symptoms are not found in papular urticaria, while they are always present in prurigo mitis. The latter disease is of much longer duration than the former.

ETIOLOGY OF PAPULAR URTICARIA AND PRURIGO MITIS

Very little is definitely known of the causes of either of these diseases. Many factors have been incriminated, such as teething, gastrointestinal disturbances, errors in diet, intestinal parasites, insect bites, contact with various substances, environmental conditions, foci of infection, rickets, tuberculosis, congenital syphilis (especially for prurigo), and many others. The association of some hereditary or acquired constitutional disturbance with the etiology of these diseases probably originated with the conception of Alibert, Bazin, Besnier, and others as to the existence of a "dartre" or diathesis in these conditions.

With the development of the subject of allergy, a number of investigations were made in an attempt to discover a possible relationship between papular urticaria and prurigo mitis, and some form of hypersensitiveness. Reports in the literature on the results of skin testing for sensitivities in these illnesses are scant and unconvincing. In some instances, Engman and Wander,[1] Low,[2] and Haxthausen,[3] the cutaneous tests were all negative. In other reports, Low,[4] Hallam,[5] Karplus,[6] Corson, Perlman, Waltz, and Ash,[7] the skin tests were positive to one or more substances, but their elimination had no effect on the illnesses. On the other hand, some investigators reported that patients with those diseases were cured or greatly relieved of their symptoms by the elimination of the substances giving the positive skin reactions. Such experiences were noted by Sidlick and Knowles,[8] Pehu and Simitch,[9] del Vivo,[10] Pasteur, Vallery-Radot and Heimann,[11] Bray,[12] and others. Urbach,[13] although he doubted the value of the skin tests, believed that all papular urticarias were "alimentary idiosyncratic dermatoses." He reported cures in his cases by dietetic regulation, which consisted of the elimination of the suspected foods and the subsequent feeding of them in association with their corresponding "propeptans."

In view of the above conflicting and inadequate reports on these diseases, we, in seeking further information on this subject, made a study of a series of patients with papular urticaria and prurigo mitis. As will be noted from the report which follows, we attempted a more detailed and varied study than those of previous workers.

SCOPE OF THE INVESTIGATION

The patients employed in this investigation were all children and were obtained from the dermatology, allergy, and pediatric clinics. Those who showed seborrheic dermatitis, dermatophytosis, or other cutaneous diseases associated with the papular urticaria, or the prurigo, were not included in the series. Studies were begun on about 75 patients, but for various reasons were completed in only 41. The final total included 36 cases of papular urticaria and 5 of prurigo mitis.

A detailed history was taken in every case, special emphasis being placed on all factors which have hitherto been suggested as of possible etiologic significance. Accordingly, thorough inquiry was made concerning the personal or familial history of atopy. Previous illnesses and their bearing on the onset or aggravation of the symptoms were noted. Search for dietetic disturbances in relation to the eruption was made in every instance. Contact and environmental factors, such as bedding, clothing, soap, animals, water supply,* residential locations, and other leads toward a possible etiology were carefully considered.

Complete physical examinations, including a search for foci of infection, were made in every patient. Repeated urinalyses, blood counts, stool examinations for ova and parasites, tuberculin tests, cutaneous tests for hypersensitiveness, and other special investigations were made as the occasion demanded.

The patients were then placed on treatment. This consisted of the elimination from the diet of all substances which gave positive cutaneous reactions. Inhalants and contactants, such as feathers, insecticides, silks, and others which reacted positively, were also removed from the patients' environment.

Additional therapeutic means were instituted. Skin irritants such as the use of soaps, liniments, excessive bathing, etc., were prohibited. Sleeping arangements and general surroundings were improved wherever possible. All drugs such as aspirin, phenolphthalein, bromides, and others were forbidden. Possible foci of infection were treated. Nonspecific therapy in the form of injections of vaccine and of dust was instituted in a number of patients. Infra-red and ultraviolet ray exposures were also employed.

The period of observation of these patients ranged from two months to three and one-half years. The following case reports are examples of the type of cases employed in these studies, and the nature of the investigations made upon them.

CASE 1.—L. E., seven and one-half years of age with papular urticaria (Table I, Case 15).

Chief complaint.—A rash on the body for five years.

Family history.—A maternal uncle has hay fever.

Past personal history.—The patient was subject to occasional upper respiratory infections. His tonsils and adenoids had been removed at five years of age. He gave no personal history of allergy.

Present illness.—The eruption began at the age of two and one-half years with "swellings" on the face, arms, legs, and trunk. The rash lasted several days, and recurred in crops. Toward the winter, the eruption gradually diminished, and left small pigmented spots. During the ensuing four summers, similar recurrences took place. There were no new eruptions during the winter.

*A study of the water supply in relationship to the etiology of these illnesses was attempted. The multiplicity of sources of water used in New York City, however, prevented the completion of these investigations.

TABLE 1

SUMMARY OF FINDINGS

PAPULAR URTICARIA

CASE NO.	NAME	SEX	AGE	FAMILY HISTORY OF ALLERGY	PERSONAL HISTORY OF ALLERGY	AGE OF ONSET	SEASONAL INCIDENCE	PERIOD OF OBSERVATION	EOSINOPHILE COUNT	TUBERCULIN TEST	POSITIVE REACTIONS BY DIRECT TESTING	POSITIVE REACTIONS BY INDIRECT TESTING
1.	R. S.	F.	4 yr.	Asthma in grandparent		8 mo.	persistent	4 mo.	3%		none	none
2.	F. M.	F.	4 yr.	Asthma in grandparent; infantile eczema in cousin		13 mo.	summer	2 mo.	1%		green pea, feathers, oats, string bean, silkworm	feathers
3.	K. L.	F.	5 yr.			3 yr.	summer	10 mo.	2%		none	
4.	K. M.	M.	4½ yr.	Asthma in grandparent		9 mo.	summer	4 mo.	11%		dust, feathers	feathers, dust, string bean, spinach, pyrethrum
5.	M. M.	F.	4½ yr.			4 yr.	summer	2 mo.	4½%		none	
6.	B. G.	M.	6 yr.	Hay fever in uncle		6 mo.	summer	4 mo.	8%		feathers, dust	feathers, dust
7.	F. M.	F.	3½ yr.			18 mo.	summer	6 mo.	3½%		none	
8.	G. T.	F.	3 yr.	Asthma in grandparent	Angioneurotic edema and asthma	3 mo.	persistent	1 yr.	3%		chicken, wheat, herring, spinach, carrots, feathers, salmon	
9.	K. F.	F.	1¾ yr.			15 mo.	summer	6 mo.	2%		none	
10.	K. I.	F.	2½ yr.			18 mo.	summer	3 mo.	2%		none	
11.	C. S.	M.	5½ yr.			3½ yr.	summer	6 mo.	0%	negative	none	
12.	S. G.	F.	1½ yr.			11 mo.	persistent	11 mo.	6%	negative	none	
13.	R. E.	M.	2 yr.	Hay fever in uncle		15 mo.	summer	5 mo.	6%	negative	none	
14.	G. F.	F.	3 yr.	Asthma in cousin; urticaria in father		2¾ yr.	persistent	5 mo.	1%	negative	none	

TABLE I—CONT'D

15.	L. E.	M.	7½ yr.	Hay fever in uncle		2½ yr.	summer	11 mo.	2%		none	none
16.	H. B.	F.	7 yr.			10 mo.	persistent	13 mo.	4%		none	none
17.	G. F.	M.	3 yr.	Asthma in grandparent	Asthma	2 yr.	persistent	18 mo.	3%	negative	dust, feathers, mustard	plantain, mustard, ragweed
18.	A. M.	M.	11 yr.			1 yr.	persistent	3 mo.	2%		none	
19.	M. B.	M.	2 yr.			1 yr.	persistent	6 mo.	10%	negative	none	
20.	B. M.	M.	2 yr.			18 mo.	summer	6 mo.	4%		none	
21.	S. C.	F.	8 yr.			2½ yr.	summer	12 mo.	4%		none	none
22.	M. M.	F.	1½ yr.			13 mo.	persistent	2 mo.	6%		none	
23.	G. S.	M.	3 yr.			2¾ yr.	persistent	15 mo.	2½%		none	
24.	F. B.	F.	4 yr.			18 mo.	persistent	3 mo.	2%		none	
25.	H. S.	M.	3 yr.	Hay fever in aunt and cousin	Infantile eczema	2 yr.	summer	4 mo.	20%		feathers, dust, grape	feathers, silkworm, grape
26.	M. S.	M.	7 yr.			8 mo.	persistent	2 mo.	3%		none	
27.	G. S.	M.	10½ yr.	Asthma in grandparent		10 yr.	persistent	3 mo.	2%		none	
28.	M. B.	M.	6 yr.			1 yr.	persistent	1 yr.	3%		none	
29.	H. E.	M.	5½ yr.			5 yr.	persistent	4 mo.	4%		none	
30.	B. R.	M.	1 yr.	Asthma in grandparent		10 mo.	persistent	4 mo.	10%		none	
31.	J. M.	F.	2½ yr.			2½ yr.	summer	10 mo.	4%	negative	none	
32.	P. F.	F.	3 yr.	Hay fever in father		2 yr.	persistent	4 mo.	6%	negative	none	none
33.	Y. P.	M.	2 yr.	Asthma in cousin	Infantile eczema	21 mo.	persistent	3 mo.	29%		dust, feathers, wheat, chicken, rye	dust, feathers, wheat, corn, rice, rye, pineapple
34.	S. L.	F.	5 yr.	Asthma in grandparent; eczema in cousin		2 yr.	summer	11 mo.	4%		none	

TABLE I—CONT'D

CASE NO.	NAME	SEX	AGE	FAMILY HISTORY OF ALLERGY	PERSONAL HISTORY OF ALLERGY	AGE OF ONSET	SEASONAL INCIDENCE	PERIOD OF OBSERVATION	EOSINOPHILE COUNT	TUBERCULIN TEST	POSITIVE REACTIONS BY DIRECT TESTING	POSITIVE REACTIONS BY INDIRECT TESTING
35.	D. J.	M.	7½ yr.	Asthma in grandparents	Infantile eczema	18 mo.	summer	4 mo.	2%	negative	silkworm, dust, spinach	silkworm, dust, spinach, wheat, orange, wool, carrot
36.	J. L.	M.	7½ yr.	Asthma in father	Infantile eczema and asthma	1 yr.	summer	2½ yr.	23%	negative	flaxseed, wheat, buckwheat, barley, flounder, salmon, herring, chicken, tomato, green pea, plantain, feathers, goat epithelium	corn, buckwheat, wheat, rice, barley, rye, string bean, spinach, lamb, timothy, ragweed, goat epithelium, miscellaneous epithelia (horse, cat, dog, rabbit), wool, plantain
					PRURIGO MITIS (KAPOSI)							
37.	R. S.	M.	3 yr.	Hay fever in grandparent		6 mo.	persistent	4 mo.	4%	negative	none	dust
38.	C. T.	F.	10 yr.	Asthma in grandparent; asthma and hay fever in mother		1 yr.	persistent	18 mo.	3%	negative	none	
39.	K. M	M.	5 yr.	Asthma in grandparent; infantile eczema in sister	Infantile eczema and asthma	11 mo.	persistent	3½ yr.	4%		wheat, chocolate	chocolate, dust, orange, banana, tomato, cottonseed, orris, wool, olive, goat epithelium, feathers, trees
40.	G. N.	M.	5½ yr.	Asthma in grandparent		6 mo.	persistent	14 mo.	3%	negative	none	none
41.	B. B.	M.	9 yr.	Asthma in father	Asthma	1 yr.	persistent	3½ yr.	7%		none	dust, goat epithelium

Physical examination.—A general physical examination was essentially negative. The skin showed a papular urticaria involving the extremities, face, and trunk. The eruption was very pronounced on the extremities. Scarring and enlarged glands were absent.

Laboratory examinations.—Frequent urine examinations showed no abnormalities. The stools were negative for ova and parasites. The blood showed a normal differential count, with 2 per cent eosinophiles.

Skin testing.—The direct and the indirect tests were negative.

CASE 2.—G. T., three years of age, with papular urticaria and asthma (Table I, Case 8).

Chief complaint.—A rash on the body since three months of age.

Family history.—A maternal grandfather had asthma.

Past personal history.—The patient had chickenpox at the age of two years. She gave no personal history of allergy.

Present illness.—The rash appeared as "red blotches coming and going," limited at first to the extremities, but later extended to the trunk. The eruption never cleared up entirely. The symptoms were worse during the winter.

Physical examination.—Aside from the dermatologic condition, physical examination was negative. The skin showed a general papular urticaria in all stages of development, especially marked on the extremities. There was no scarring, and no glands were palpable.

Laboratory examinations.—The urinalyses were repeatedly negative. The stools were negative for ova and parasites. The blood showed a normal differential count with 3 per cent of eosinophiles.

Skin testing.—The direct method revealed positive reactions to chicken, wheat, herring, spinach, carrots, feathers, and salmon.

Clinical course.—Dietary elimination did not influence the course of the papular urticaria. While under observation, the patient had an attack of angioneurotic edema of the face caused by eating smoked white fish. While under treatment for the papular urticaria the patient developed asthma which was controlled under a rigid dietetic regime, but the papular urticaria persisted.

CASE 3.—G. N., five and one-half years of age, with prurigo mitis (Table I, Case 40).

Chief complaint.—A rash over the body for five years.

Family history.—A paternal grandmother has asthma.

Past personal history.—The patient had measles at the age of one and one-half years. He had frequent attacks of bronchitis and tonsillitis. There was no personal history of allergy.

Present illness.—At the age of six months, the patient had an attack of "hives," which lasted about six months. The rash recurred the following summer, and persisted, the lesions becoming more numerous and more itchy. The symptoms were worse during the hot weather.

Physical examination.—The child was undernourished, and showed a profuse eruption of papules, many of them scratched off, bleeding or crusted. Lichenification, pigmentation, scars, and markedly enlarged cervical, axillary and inguinal glands were also present. The lesions were especially pronounced on the extremities.

Laboratory examinations.—A number of urinalyses were negative. The stools were negative for ova or parasites. Blood counts showed 3 per cent eosinophiles.

Skin testing.—The direct and the indirect tests were negative.

CASE 4.—K. M., five years of age, with prurigo mitis and asthma. (Table I, Case 39.)

Chief complaint.—Rash on the body and extremities for about four years.

Family history.—A maternal grandfather had asthma, and one sister aged two and a half months has eczema.

Past personal history.—Up to six months of age the patient had an eczema of the face.

Present history.—An eruption of "red lumps with white centers," very itchy, appeared on the trunk and extremities, after the facial eczema had cleared up (during the first year). This condition kept recurring in crops with no special seasonal predilection.

Physical examination.—A complete physical examination yielded negative findings except for the skin condition. The extremities especially showed many scratched-off, bleeding and crusted papules, intermingling with new papules. Lichenification and pigmentation were pronounced on the forearms and legs. Tiny scars were prevalent on the extremities. The trunk showed scattered, scratched-off papules with a few scattered scars. The inguinal and axillary glands were enlarged.

Laboratory examinations.—Urine examinations were negative. The stools were negative for ova and parasites. The blood counts showed 4 per cent eosinophiles.

Skin testing.—The direct method gave positive reactions to wheat and chocolate.

Clinical course.—The elimination of wheat and chocolate from the diet over a period of several months had no influence on the prurigo mitis. The patient later developed recurring attacks of rhinitis, cough, and heaviness in breathing. The eruption remained more or less persistent.

About two weeks following the appearance of the respiratory symptoms (bronchial asthma), testing by the indirect method was done. This revealed positive reactions to chocolate, dust, banana, orange, tomato, cottonseed, orris, wool, olives, goat epithelium, and feathers. The patient returned only a few times thereafter, and the subsequent course of the prurigo mitis and the asthma was not noted.

SUMMARY OF FINDINGS

In the series of 36 papular urticarias, 17 (47 per cent) were females and 19 (53 per cent) were males. The ages ranged from one to eleven years, the average being about four and one-half years. Of the five prurigos, four were males and one female. Their ages varied from three to ten years.

In the urticarial group, 17 patients (47 per cent) gave a positive family history of atopy, and of these six presented past or present personal histories of atopy such as infantile eczema or asthma (Table II, Cases 8, 17, 25, 33, 35 and 36). Among the prurigos, all revealed family histories of atopy, and two patients also gave a past and a present history of infantile eczema and of asthma (Table II, Cases 39 and 41).

The age of onset in the papular urticarias, ranged from six months to ten years, with an average of twenty-two and one-half months. In half of the patients, the lesions persisted perennially, and in the remainder they appeared only during the summer. The age of onset among the prurigos ranged from six months to a year, with an average of nine and two-fifths months. In all of these cases the lesions were persistent throughout the year.

TABLE II

CASES WITH POSITIVE ATOPIC HISTORIES AND RESULTS OF SKIN TESTS

			POSITIVE HISTORY OF ATOPY								SKIN TESTS	
			FAMILIAL									
		CASE NO.	FATHER	MOTHER	SISTER	GRAND-PARENT	UNCLE	AUNT	COUSIN	PERSONAL	DIRECT METHOD	INDIRECT METHOD
PAPULAR URTICARIA	1	1				asthma					negative	negative
	2	2				asthma			infantile eczema		positive	positive
	3	4				asthma					positive	positive
	4	6					hay fever				positive	positive
	5	8				asthma				asthma, angioneurotic edema	positive	
	6	13					hay fever				negative	
	7	14	urticaria						asthma		negative	
	8	15					hay fever				negative	negative
	9	17				asthma				asthma	positive	positive
	10	25						hay fever	hay fever	infantile eczema	positive	positive
	11	27				asthma					negative	
	12	30				asthma					negative	
	13	32	hay fever								negative	negative
	14	33							asthma	infantile eczema	positive	positive
	15	34				asthma			infantile eczema		negative	
	16	35				asthma				infantile eczema	positive	positive
	17	36	asthma		—					infantile eczema, asthma	positive	positive
PRURIGO MITIS (KAPOSI)	1	37				hay fever					negative	positive
	2	38		asthma, hay fever		asthma					negative	
	3	39			infantile eczema	asthma				infantile eczema	positive	positive
	4	40				asthma					negative	negative
	5	41	asthma							asthma	negative	positive

Complete physical examinations revealed no marked or constant abnormalities, with the exception of an occasional suspected focus of infection, such as diseased tonsils or sinusitis. Repeated routine urinalyses gave negative findings in all instances. The intradermal tuberculin test (1:1,000) was performed in 13 patients; the results were uniformly negative. Routine stool examinations for ova and parasites gave entirely negative findings. Differential blood counts, exclusive of eosinophilia, were within normal limits. The eosinophile count in the 36 papular urticarias ranged from 0 per cent to 29 per cent, with an average of 5.66 per cent (Tables I and III). In the prurigo group of five patients, the count varied from 3 per cent to 7 per cent, averaging 4.25 per cent. A more detailed summary of the eosinophile findings and their significance will be discussed shortly.

All 41 cases were tested intracutaneously by the direct method of Cooke. In addition, 13 papular urticarias and 4 prurigos were tested by the indirect method of Walzer.[14] Only 12 patients (9 papular urticarias and 3 prurigos) gave positive reactions by either or both methods (Tables I and II, Cases 2, 4, 6, 8, 17, 25, 33, 35, 37, 39, 41). Twenty-nine patients (27 papular urticarias and 2 prurigos) revealed no positive reactions by either method of cutaneous testing. About 60 atopens were employed in these tests. The following lists give all those demonstrating positive reactions by either method of testing, together with their frequency of occurrences. The direct method of testing showed: feathers (chicken, duck, and goose), 8; house dust, 6; wheat, 4; chicken meat, 3; spinach, 2; silkworm, 2; herring, 2; green pea, 2; salmon, 2; cat epithelium, 1; string bean, 1; mustard, 1; rye, 1; chocolate, 1; goat epithelium, 1; buckwheat, 1; tomato, 1; barley, 1; plantain pollen, 1; carrot, 1; flaxseed, 1; flounder, 1.

The indirect method of testing showed: house dust, 7; feathers (chicken, duck and goose), 6; wheat, 3; spinach, 3; goat epithelium, 3; wool, 3; silkworm, 2; string bean, 2; rye, 2; plantain pollen, 2; orange, 2; corn, 2; rice, 2; oat, 1; herring, 1; mustard, 1; chocolate, 1; banana, 1; cottonseed, 1; olive, 1; tree pollens, 1; grape, 1; lamb, 1; miscellaneous animal danders, 1; timothy pollen, 1; ragweed pollen, 1; buckwheat, 1; tomato, 1; barley, 1; pyrethrum, 1; pineapple, 1.

RESULTS OF TREATMENT

The institution of specific treatment which consisted of the elimination of all positively reacting substances, either dietetic, inhalant, or contactant, was of no avail. In no instance was there any improvement or relief obtained as a result of these measures. No causal relationship could be established between the substances giving positive skin tests and the papular urticaria or the prurigo. Moreover, none of the additional therapeutic procedures previously mentioned (such as correction of foci of infection, physiotherapy, elimination of skin

irritants, and others) can be said to have influenced favorably the course of the illness.

DISCUSSION

Relation of Heredity to Papular Urticaria and Prurigo Mitis

Of the 36 cases of papular urticaria, 19 (53 per cent) gave a negative familial history of atopy. The remaining 17 (47 per cent) revealed histories of hay fever, asthma, or infantile eczema in the family (Table II); among the latter were six patients (Cases 8, 17, 25, 33, 35, 36) who gave histories of past or present personal atopy (asthma in Cases 8, 17, and 36 and infantile eczema in Cases 25, 33, 35, and 36). All five cases of prurigo revealed a familial history of hay fever and asthma. Two patients (Cases 39 and 41) gave a previous personal history of atopy (infantile eczema, in Case 39 and asthma in Case 41).

The high incidence of positive family histories of atopy and of associated atopic illnesses in patients with papular urticaria, strongly suggests that these illnesses are also atopic in nature. A positive atopic family history of 47 per cent in papular urticaria is only slightly lower than the average of many tabulations in asthma, which is about 50 per cent. It must be remembered, moreover, that the patients studied consisted entirely of children varying from one to eleven years of age. It is quite probable that were they to be observed at intervals later in life, a gradually increasing number of them would be found to have developed atopic illnesses, such as hay fever and asthma.*

Since only five patients with prurigo were studied, definite conclusions from such a small number cannot be drawn. The presence of a positive family history of atopy in every instance, however, suggests the probability of an atopic basis for this disease as well.

Whether papular urticaria and prurigo mitis are necessarily the result of some form of hypersensitiveness is still a question to be determined. As has been pointed out by Coca[15] and his associates, the atopic shock organ may be stimulated nonspecifically, and this possibility must be entertained in relation to these diseases where no etiology or known form of hypersensitive mechanism has as yet been found. Doubt as to the presence of such a mechanism in these illnesses is further justified by the fact that their lesions manifest productive inflammatory changes, whereas all known forms of atopic hypersensitiveness exhibit only a transient, nonproductive inflammatory process.

Relation of Skin Tests to Papular Urticaria and Prurigo Mitis

Twenty-seven (75 per cent) of the papular urticarias gave entirely negative skin reactions. This group comprised 19 cases with negative

*Since this writing, this contention has been substantiated by the subsequent development of atopic symptoms, such as hay fever and asthma, in some of these patients.

family histories of atopy and 8 with positive histories. Nine papular urticarias (25 per cent) of this series gave positive skin tests. Among the patients with prurigo, 3 of the 5 manifested positive skin reactions, although all gave positive family histories of atopy. Of the 3 with positive reactions, 2 presented personal past histories of atopy (Table II, Cases 39 and 41).

In not a single instance could any association be detected between any of the excitants giving positive cutaneous reactions and the papular urticaria and prurigo. Neither the removal of the positively reacting foods from the diet, nor their inclusion had any influence on the course of these diseases in any patient. The same conclusion was drawn concerning the etiologic significance of the positively reacting inhalants and contactants in these cases.

As these positive reactions were obtained in most instances by both the direct and the indirect method of testing, their reliability could not be doubted.* It is significant that all of the 12 cases (9 papular urticarias, and 3 prurigos) presenting positive cutaneous reactions had a positive family history of atopy, and in eight instances (Cases 8, 17, 25, 33, 35, 37, 39, 41) a past or present personal history of atopic illnesses such as asthma or infantile eczema. Every indication therefore points to the probability that the cutaneous reactions in each instance could be linked to the latter diseases rather than to the papular urticaria or prurigo. In those patients with an associated asthma this relationship was quite obvious. In those with a past history of infantile eczema, the positive reactions undoubtedly pertained to this earlier hypersensitiveness. Since the patients under consideration were all under eleven years of age, it seems very plausible that other allergic symptoms to which some of these positive reactions might be related, might yet develop in a number of the patients.

Relation of Eosinophile Count to Skin Tests and Hereditary History

Analysis of the eosinophile counts in the above series of cases reveals that 5.66 per cent was the average for the entire series of papular urticarias (Table III). The 19 cases with negative family histories of atopy showed an average of 3.6 per cent eosinophiles. The 17 patients with positive family histories of atopy demonstrated an average eosinophile count of 8 per cent (Table III). The nine patients with positive skin reactions in the latter group averaged 11 per cent, while the eight with negative reaction averaged 4.25 per cent. The highest eosinophile count, 13.33 per cent, was found in the six patients with papular urticaria who presented past or present personal atopic mani-

*A comparison of the results of testing by the direct and indirect methods, and the significance of the above findings from the point of view of testing technic, will be the subject of another communication, and will, therefore, not be discussed at this time.

festations. The largest group of papular urticaria, the 27 who gave negative skin reactions, showed an average eosinophile count of 3.8 per cent.

TABLE III

GROUPING OF THE CASES AND THE EOSINOPHILE COUNT

PAPULAR URTICARIA	NUMBER AND PERCENTAGE		EOSINOPHILIA
Total Number of Cases	36		5.66%
I. Cases with negative family history of atopy	19	53%	3.6 %
II. Cases with positive family history of atopy	17	47%	8.0 %
A. Cases with negative skin tests	8	22%	4.25%
B. Cases with positive skin tests	9	25%	11.0 %
1. Cases with personal history of atopy	6	16%	13.33%
2. Cases without personal history of atopy	3	9%	6.66%
III. Cases with Negative Skin Tests	27	75%	3.8 %
PRURIGO MITIS			
Total Number of Cases	5		4.25%
I. Cases with positive family history of atopy	5		4.25%
A. Cases with positive skin tests	3		
1. Cases with personal history of atopy	2		

A review of these figures (Table III) would seem to indicate that the eosinophile count was increased in those cases of papular urticaria in whom such factors as positive family history of atopy (8 per cent eosinophiles), positive skin tests (11 per cent eosinophiles), and positive personal histories of atopy (13.33 per cent eosinophiles) were present. The average count of 3.8 per cent representing the large group of 27 cases which showed no positive skin reactions, would appear to be more characteristic of uncomplicated papular urticaria.

The prurigos showed an average eosinophile count of 4.25 per cent. This series is too small, however, to justify any conclusion.

SUMMARY

1. Forty-one patients, 36 with papular urticaria and 5 with prurigo mitis (Kaposi) were thoroughly studied and subjected to direct and indirect tests for the detection of possible sensitivities.

2. Seventeen (47 per cent) of the papular urticarias and all of the prurigos gave positive family histories of atopy. Among the above papular urticarias were six who also gave past or present personal histories of atopy (asthma and infantile eczema).

3. Positive skin tests to one or more atopens were obtained only in the group of papular urticarias that demonstrated positive family histories of atopy. They were found only in nine patients (25 per cent of the entire series of papular urticarias). Among these nine were the six patients who gave past or present personal histories of atopy.

Among the prurigos, three of the five cases gave positive cutaneous reactions and all revealed positive family histories of atopy.

4. An increased eosinophile count was usually found to be associated with a positive family or personal history of atopy and with positive skin tests. It was apparently not the result of the papular urticaria. A count of 3.8 per cent was the average for the simple uncomplicated papular urticarias. The eosinophile count in the prurigos varied from 3 to 7 per cent.

5. Attempts at specific therapy, as suggested by the positive skin tests, and at nonspecific therapy were of no value in the treatment of papular urticaria or prurigo mitis.

CONCLUSIONS

1. Papular urticaria and prurigo mitis (Kaposi) are probably atopic illnesses.

2. Positive skin tests obtained in patients with papular urticaria and prurigo mitis bear no relation to these illnesses, but pertain to other atopic conditions associated with them. Skin testing in papular urticaria and prurigo mitis is of no diagnostic or therapeutic value.

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ACTIVE SENSITIZATION IN HUMAN BEINGS*†

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WALZER[1, 2] and his coworkers demonstrated by a special technic that in most normal human beings the gastrointestinal tract is permeable to protein in an unaltered state. Hence the blood stream is being constantly invaded by antigenic substances which have been ingested and also, as Cohen and his coworkers[3] subsequently showed, by antigens which are absorbed through the respiratory tract; yet only 7 per cent of the white population of this country are atopic, and not all of these manifest sensitivity to the common atopens. It would seem, therefore, that antigenic stimulation alone would not satisfactorily explain the development of atopic hypersensitiveness.

The production of atopic reagins as a result of unusual antigenic stimulation is a frequent occurrence in normal, i.e., nonatopic individuals. Cooke and Spain[4] reported the production of skin sensitizing reagins in a nonatopic person following the injection of horse serum. Tuft[5] showed that following the injection of horse serum or insulin in nonatopic persons, skin reactions and the production of reagins and precipitins resulted in a certain percentage of cases and that these phenomena were only transient.

Fulleborn and Kikuth[6] induced skin sensitiveness after two weeks in a non-sensitive person by the injection of ascaris extract. This persisted for six months. Coca[7] reported a similar observation in one instance.

The anti-ascaris reagins were first demonstrated by Rackemann and Stevens[8] and were shown by Brunner,[9] Fulleborn, and others to be present in all cases in which a marked immediate positive skin test was present. This occurred in both atopic and nonatopic individuals.

The present work was undertaken to determine whether human beings could be actively sensitized, like the experimental animal, by repeated subcutaneous injections of various excitants, and if this could be accomplished, to study the nature of such an induced sensitivity.

Out of a series of 40 human beings consisting of atopic and nonatopic individuals, into whom one or more antigens were injected subcutaneously over variable periods of time, 15 cases were selected for this report. They represent those cases which were treated most intensively and were observed the longest.

The individual case reports are presented herewith and the results tabulated in Table I.

*From the Department of Allergy of the Brooklyn Jewish Hospital.
†Read before the Society for the study of Asthma and Allied conditions at Atlantic City, May, 1931.

TABLE I

CASE	AGE	ATOPIC FAMILY HISTORY	ATOPIC PERSONAL HISTORY	CLINICAL SYMPTOMS	SPECIFIC NATURAL SENSITIVITY	ATOPEN INJECTED SUBCUTANEOUSLY	CONCENTRATION OF ATOPEN IN MG. N (B) PER C.C.	NO. INJECTIONS	SIZE OF DOSE IN C.C.	TOTAL QUANTITY INJECTED IN C.C.	PERIOD OF TREATMENT IN WEEKS	FINAL SKIN TEST WITH SOLUTION 0.1 MG. N (B) PER C.C.	PRAUSNITZ-KÜSTNER TEST	SKIN TEST WITH SOLUTION ./ MG. N (B) PER C.C. AFTER 1 TO 2 YEARS
1	43	Denied	Positive	Hay fever	Ragweed pollen	Orris	0.1	11	0.1-0.2	1.9	11	Negative		
						Rabbit ep. (b)	0.1	11	0.1-0.2	1.9	11	Negative		
2	32	Denied	Positive	Hay fever	Ragweed pollen	Orris	0.1	14	0.1-0.4	3.7	18	Negative		
						Rabbit epithelium	0.1	14	0.1-0.4	3.7	18	Negative		
3	40	Denied	Positive	Hay fever	Ragweed pollen	Orris	0.1	12	0.1-0.3	2.5	16	Negative		
					Timothy pollen	Rabbit epithelium	0.1	12	0.1-0.3	2.5	16	Negative		
4	12	Denied	Positive	Asthma	Chicken epithelium	Orris	0.1	20	0.1-0.5	2.6	9	Negative		
				V.M.R. (a)	Goat epithelium	Rabbit epithelium	0.1	20	0.1-0.5	5.7	20	Negative		
					Dust									
5	17	Positive	Positive	Hay fever	Ragweed pollen	Orris	0.1	15	0.1-0.6	6.3	15	Positive	Pos.	Negative
				Asthma	Rabbit epithelium									
6	33	Positive	Positive	Asthma	Orris	Egg	0.1	19	0.1-2.0	18.1	24	Negative		
				V.M.R. (a)										
7	35	Denied	Positive	Asthma	Ragweed pollen	Egg	0.1	16	0.1-2.0	18.0	23	Negative		
				Hay fever		Rabbit epithelium	0.1	16	0.1-0.5	4.5	23	Negative		

(a) Vasomotor rhinitis. (b) N—Nitrogen.

TABLE I—CONT'D

CASE	AGE	ATOPIC FAMILY HISTORY	ATOPIC PERSONAL HISTORY	CLINICAL SYMPTOMS	SPECIFIC NATURAL SENSITIVITY	ATOPEN INJECTED SUBCUTANEOUSLY	CONCENTRATION OF ATOPEN IN MG. N (B) PER C.C.	NO. INJECTIONS	SIZE OF DOSE IN C.C.	TOTAL QUANTITY INJECTED IN C.C.	PERIOD OF TREATMENT IN WEEKS	FINAL SKIN TEST WITH SOLUTION 0.1 MG. N (B) PER C.C.	PRAUSNITZ-KÜSTNER TEST	SKIN TEST WITH SOLUTION ./. MG. N (B) PER C.C. AFTER 1 TO 2 YEARS
8	55	Denied	Negative	Asthma	Negative	Egg	0.1	48	0.5-2.0	64.5	32	Negative		
9	35	Denied	Negative	Asthma	Negative	Egg	0.1	16	1.0	16.0	10	Negative		
						Rabbit epithelium	0.1	16	0.1-0.5	4.2	10	Negative		
						Orris	0.1	16	0.1-0.5	4.2	10	Negative		
10	22	Denied	Positive	Hay fever	Ragweed pollen	Egg	0.1	19	0.1-2.0	35.0	17	Negative		
						Rabbit epithelium	0.1	14	0.1-0.3	3.3	17	Negative		
						Orris	0.1	14	0.1-0.3	3.3	17	Negative		
11	38	Denied	Negative	Asthma	Negative	Ascaris	0.01	10	0.1-1.0	7.1	17	Negative		
12	30	Denied	Positive	Hay fever	Ragweed pollen	Ascaris	0.01	6	0.1-0.4	1.5	4	Positive	Pos.	Negative
13	51	Denied	Positive	Asthma	Rabbit epithelium	Ascaris	0.1	6	0.1-0.2	0.9	10	Positive	Pos.	Negative
						Egg	0.1	10	1.0-2.0	10.0	10	Negative		
14	30	Positive	Positive	Hay fever Asthma	Timothy pollen	Ascaris	0.1	4	0.1	0.4	4	Positive	Pos.	Negative
						Rabbit epithelium	0.1	11	0.1-0.3	2.6	12	Negative		
						Orris	0.1	11	0.1-0.3	2.6	12	Negative		
15	25	Denied	Positive	V.M.R. (a)	Negative	Ascaris	0.01	7	0.1-1.0	3.6	5	Negative		
						Ascaris	0.1	10	0.1-0.4	2.4	9	Negative		
						Egg	0.1	32	1.0-2.0	36.5	20	Negative		
						Cat dander	0.1	25	0.1-1.0	22.3	18	Negative		

(a) Vasomotor rhinitis. (b) N—Nitrogen.

CASE 1.—Patient, aged forty-three years, gave a negative family history of atopy and a personal history of ragweed hay fever. Patient was given 11 injections of orris root extract containing 0.1 mg. nitrogen per c.c., over a period of eleven weeks. The dose varied from 0.1 to 0.2 c.c., so that the total quantity injected was 1.9 c.c. Rabbit epithelium was also given at the same time and in the same amount. The final skin tests with solutions containing 0.1 mg. N. per c.c. were negative with both extracts.

CASE 2.—Patient, aged thirty-two years, gave a negative atopic family history and a positive personal history of ragweed hay fever. Patient was given 14 injections of orris root extract, containing 0.1 mg. N. per c.c., over a period of eighteen weeks. The dose varied from 0.1 to 0.4 c.c., so that the total quantity injected was 3.7 c.c. Rabbit epithelium extract in the same dosage was also given at the same time. The final skin tests with solutions containing 0.1 mg. N. per c.c. were negative with both extracts.

CASE 3.—Patient, aged forty years, gave a negative atopic family history, and a positive personal history of timothy and ragweed hay fever. Patient was given 12 injections of orris root extract, containing 0.1 mg. N. per c.c., over a period of sixteen weeks. The dose varied from 0.1 to 0.3 c.c., so that the total quantity injected was 2.5 c.c. Rabbit epithelium extract in the same dosage was also given at the same time. The final skin tests with solutions containing 0.1 mg. N. per c.c. were negative with both extracts.

CASE 4.—Patient, aged twelve years, gave a negative atopic family history, had a personal history of vasomotor rhinitis and asthma, and manifested positive cutaneous reactions to chicken epithelium, dust and goat epithelium. Twenty injections of orris root extract, containing 0.1 mg. N. per c.c., were given over a period of nine weeks. The dose varied from 0.1 to 0.5 c.c., so that the total quantity injected was 2.6 c.c. A total of 5.7 c.c. of rabbit epithelium extract, in a concentration of 0.1 mg. N. per c.c. was also given in doses varying from 0.1 to 0.5 c.c., over a period of twenty weeks. The final skin tests with the solutions containing 0.1 mg. N. per c.c. were negative with both extracts.

CASE 5.—Patient, aged seventeen years, gave a positive atopic family history of asthma, had a personal history of hay fever and asthma, and gave positive reactions to ragweed pollen and rabbit epithelium. Fifteen injections of orris root extract, containing 0.1 mg. N. per c.c. were given in doses of 0.1 to 0.6 c.c., so that the total quantity injected was 6.3 c.c. A severe local reaction occurring within twenty-four hours after the 15th injection suggested the possible presence of an induced sensitivity. A final skin test performed ten days later with a solution containing 0.1 mg. N. per c.c. was positive. This positive skin reaction was transferable by the Prausnitz-Küstner technic. (See Table II.)

TABLE II

	DATE OF INJECTION	NO. OF C.C. INJECTED OF ORRIS 0.1 MG. N PER C.C.	INTRACUTANEOUS TEST WITH ORRIS 0.1 MG. N PER C.C.
1	2/ 1/30	0.1	Negative
2	2/ 8/30	0.2	
3	2/15/30	0.3	
4	3/ 1/30	0.3	
5	3/ 7/30	0.3	
6	3/15/30	0.4	
7	3/22/30	0.5	
8	3/29/30	0.5	
9	4/ 5/30	0.5	
10	4/12/30	0.5	
11	4/19/30	0.5	
12	4/26/30	0.6	
13	5/17/30	0.5	
14	5/24/30	0.5	
15	5/31/30	0.6	
	6/11/30		Marked positive*
	8/31/31		Negative
Total amount injected of orris 0.1 mg. N per c.c.		6.3 c.c.	

*Transferred by Prausnitz-Küstner technic.

About one year later, however, the cutaneous reaction had again become negative to tests with an orris root extract containing 0.1 mg. N. per c.c.

CASE 6.—Patient, aged thirty-three years, gave a positive atopic family history, and a personal history of vasomotor rhinitis and asthma, and showed a positive reaction to orris root extract. Nineteen injections of egg extract containing 0.1 mg. N. per c.c., in doses varying from 0.1 to 2.0 c.c. were given over a period of twenty-four weeks. The total quantity injected was 18.1 c.c. The final skin test with a solution of egg extract, containing 0.1 mg. N. per c.c., was negative.

CASE 7.—Patient, aged thirty-five years, gave a negative atopic family history and a personal history of ragweed hay fever and asthma. Patient was given 16 injections of egg extract, containing 0.1 mg. N. per c.c., in doses of 1 to 2 c.c. over a period of twenty-three weeks. A total quantity of 18 c.c. of egg extract was injected. The final skin test with a solution of egg extract, containing 0.1 mg. N. per c.c., was negative.

Sixteen injections of rabbit epithelium extract, containing 0.1 mg. N. per c.c., were also given in doses of 0.1 to 0.5 c.c. over a period of twenty-three weeks. A total of 4.5 c.c. of rabbit epithelium extract was injected. The final skin test with a solution, containing 0.1 mg. N. per c.c., was negative.

CASE 8.—Patient, aged fifty-five years, gave negative atopic family and personal histories. No positive reactions were found by skin tests. Patient had clinical symptoms of asthma. Forty-eight injections of egg extract, containing 0.1 mg. N. per c.c., were given in doses of 0.5 to

2.0 c.c. over a period of thirty-two weeks. The total quantity given was 64.5 c.c. The final test with a solution of egg extract containing 0.1 mg. N. per c.c. was negative.

CASE 9.—Patient, aged thirty-five years, gave a negative atopic and personal history. No positive reactions were found by skin tests. Patient had clinical symptoms of asthma. Sixteen injections of egg extract, containing 0.1 mg. N. per c.c., were given in doses of 1.0 c.c., over a period of ten weeks. A total of 16 c.c. was injected. In addition, 16 injections of rabbit epithelium and orris root extracts each containing 0.1 mg. N. per c.c., were given in doses of 0.1 to 0.5 c.c. over a period of ten weeks. A total of 4.2 c.c. of each extract was injected. Final skin tests with solutions of egg, rabbit epithelium and orris root extracts each containing 0.1 mg. N. per c.c. were negative.

CASE 10.—Patient, aged twenty-two years, gave a negative atopic family history, and a positive personal history of ragweed hay fever. Patient was given 19 injections of egg extract, containing 0.1 mg. N. per c.c., over a period of seventeen weeks, in doses varying from 0.1 to 2.0 c.c. A total of 35 c.c. of egg extract was injected. Similarly, 14 injections of rabbit epithelium and orris root extracts each containing 0.1 mg. N. per c.c. were given in doses varying from 0.1 to 0.3 c.c., over a period of seventeen weeks. A total of 3.3 c.c. of each extract was injected. The final skin tests with extracts of egg, rabbit epithelium and orris root extracts each containing 0.1 mg. N. per c.c. were negative.

CASE 11.—Patient, aged thirty-eight years, gave a negative atopic family history. No positive reactions were obtained by skin tests. Patient had clinical symptoms of asthma and chronic bronchitis. He was given 10 injections of ascaris extract, containing 0.01 mg. N. per c.c. The doses varied from 0.1 to 1.0 c.c. so that a total of 7.1 c.c. of ascaris extract was given over a period of seventeen weeks. The final skin test with ascaris extract, containing 0.1 mg. N. per c.c., was negative.

CASE 12.—Patient, aged thirty years, with a negative atopic family history, had a personal history of ragweed hay fever. Six injections of ascaris extract containing 0.01 mg. N. per c.c. were given in doses varying from 0.1 to 0.4 c.c. so that a total of 1.5 c.c. was injected over a period of four weeks. A severe local reaction developing within twenty-four hours at the site of the last inoculation indicated that a sensitivity had developed. On testing, a positive skin test with ascaris extract containing 0.1 mg. N. per c.c. was obtained. This was transferable to normal skin by the Prausnitz-Küstner technic. About two years later a skin test with an ascaris extract containing 0.1 mg. N. per c.c. was negative.

CASE 13.—Patient, aged fifty-one years, gave a negative atopic family history. Patient had clinical symptoms of asthma and showed a positive reaction on testing with rabbit epithelium. Six injections of ascaris

extract, containing 0.1 mg. N. per c.c., were given in doses of 0.1 to 0.2 c.c. so that a total of 0.9 c.c. was injected over a period of ten weeks. A severe local reaction developing within twenty-four hours at the site of the last inoculation suggested that a sensitivity had developed. A positive skin test was then obtained on testing with ascaris extract containing 0.1 mg. N. per c.c. This reaction was transferable to the normal skin by the Prausnitz-Küstner technic. About two years later a skin test with an ascaris extract containing 0.1 mg. N. per c.c. was negative.

Likewise, 10 injections of egg extract, containing 0.1 mg. N. per c.c. were given over a period of ten weeks. A total of 10 c.c. of egg extract was thus injected. The final skin test with egg extract containing 0.1 mg. N. per c.c. was negative.

CASE 14.—Patient, aged thirty years, gave a positive family history of atopy. Patient had clinical symptoms of timothy hay fever and asthma. Four injections of ascaris extract containing 0.1 mg. N. per c.c. were given in doses of 0.1 c.c. over a period of four weeks. A total of 0.4 c.c. was injected. A severe local reaction occurring within twenty-four hours after the fourth inoculation at the site of injection suggested that sensitivity had probably developed. On testing, a positive reaction was obtained with ascaris extract, containing 0.1 mg. N. per c.c. This was transferable to normal skin by the Prausnitz-Küstner technic. About two years later, a skin test with an ascaris extract containing 0.1 mg. N. per c.c. was negative.

Likewise, 11 injections of extracts of rabbit epithelium and orris root, containing 0.1 mg. N. per c.c., were given in doses of 0.1 to 0.3 c.c., over a period of twelve weeks. A total of 2.6 c.c. of each extract was injected. The final skin tests with extracts of rabbit epithelium and orris root, each containing 0.1 mg. N. per c.c., were negative.

CASE 15.—Patient, aged twenty-five years, gave a negative atopic family history. Patient had clinical symptoms of vasomotor rhinitis. No positive reactions could be detected by skin tests. Seven injections of ascaris extract containing 0.01 mg. N. per c.c. were given in doses of 0.1 to 1.0 c.c. over a period of five weeks. A total of 3.6 c.c. was injected. The final skin test with ascaris extract, containing 0.1 mg. N. per c.c. was negative. Subsequently, 10 more injections of ascaris extract, containing 0.1 mg. N. per c.c., were given in doses of 0.1 to 0.4 c.c. over a period of nine weeks. A total of 2.4 c.c. was injected. The final skin test with ascaris extract containing 0.1 mg. N. per c.c. was again negative. Likewise, 25 injections of cat dander extract, containing 0.1 mg. N. per c.c., were given in doses of 0.1 to 1.0 c.c. over a period of eighteen weeks. A total of 22.3 c.c. was injected. The final skin test with cat extract containing 0.1 mg. N. per c.c. was negative. Similarly, 32 injections of egg extract containing 0.1 mg. N. per c.c. were given in doses of 1.0 to 2.0 c.c.

over a period of twenty weeks. A total of 36.5 c.c. was injected. The final skin test with egg extract containing 0.1 mg. N per c.c. was negative.

DISCUSSION

The sensitivities artificially induced in this series with ascaris and orris root were shown to be reaginic in nature. They were transient and disappeared in from one to two years, in contrast with naturally induced sensitivities to these same atopens which are liable to last much longer. In this respect, therefore, such active sensitization closely resembles those transient sensitivities which are occasionally encountered after injections of horse serum and insulin in nonatopic individuals.

It would appear from the above that active sensitization in human beings with atopens which are the most common offenders clinically is extremely difficult. Only one individual (Case 5), who was already clinically sensitive to several substances, was actively sensitized to orris root. Seven others, six of whom were frankly atopic, could not be sensitized to this atopen. All attempts to sensitize with such important atopens as rabbit epithelium and egg were unsuccessful.

There seems to be something in the nature of the ascaris excitant which makes sensitization with this atopen less difficult. Of five individuals injected, three were sensitized (Cases 12, 13, 14). All these subjects were atopic. Of the two in whom attempts at sensitization failed, one was atopic. It has been my experience that among individuals with ascaris, and roundworm infestations, positive reactions to tests with ascaris occur commonly among nonatopics, as well as among atopics. Hence, it appears that the peculiar nature of the ascaris extract is a more important factor than the atopic nature of the subject in the easy induction of hypersensitiveness with this atopen.

CONCLUSION

It is extremely difficult to sensitize atopic human beings actively by subcutaneous injections of atopens which are very common and important clinical offenders. In a single instance where such sensitivity appeared to be induced with orris root, it was reaginic in nature and was of relatively short duration.

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STUDIES OF THE ANAPHYLACTIC ANTIBODY*†

PARTS I, II, AND III

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THIS series of experiments was begun with the hope that they would lead to the rational specific control of human serum reactions. Coca[1] points out that in man there are delayed serum reactions, which represent the classical serum sickness, and immediate reactions, which may occur in atopic individuals who are spontaneously sensitive to horse proteins or in nonatopic individuals in response to second or third injections of horse serum. It is generally believed that the symptoms are due to a reaction between the injected horse serum, a specific antibody produced against horse serum by the patient, and the cells of the patient.

As a working hypothesis for these experiments a close analogy is assumed: first, between anaphylaxis in guinea pigs and immediate serum reactions in humans; and second, between serum sickness in rabbits[2] or guinea pigs[3] and the classical delayed serum reaction in man. Granting the validity of these analogies it would seem logical to assume that: (1) a method which would prevent anaphylaxis in the guinea pig would prevent immediate serum reactions in man; (2) a method which would abort serum sickness in rabbits or guinea pigs would abort serum sickness in humans.

Weil[4] has shown that highly sensitized guinea pigs can be protected against five to ten times the shocking dose of horse serum by first injecting serum from highly immunized rabbits. Rackemann[5] recognized the theoretical relationship between Weil's method of protecting sensitized guinea pigs and the use of anti-horse immune serum in human serum reactions, but dismissed it as being impracticable. Longcope and Rackemann[6] felt that the cessation of symptoms in human serum sickness was coincident, usually, with an abrupt rise in precipitin titer and corresponding fall in horse serum titer of the patient's blood. The protocols of Fleisher and Jones[7] show that similar changes occur in the blood of rabbits recovering from serum sickness, but they do not call attention to it. Fleisher[8] does not think these changes significant be-

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cause rabbits which do not have evidences of serum sickness have identical changes in precipitin and horse serum titer. It cannot be denied, however, that in their experiments the precipitin titers went up and the horse serum titers went down soon after the cessation of symptoms. MacKenzie and Fruhbauer[9] observed, in human beings, that horse serum disappeared rapidly when the anti-horse serum precipitin titer reached its peak in individuals with severe serum sickness. They observed further, that in mild cases the precipitin titer was lower and the horse serum persisted longer. They were unable to cause the prompt disappearance of horse serum in rabbits by injecting large amounts of anti-horse immune serum during the first two days after injecting the horse serum. They did show that there was a slight decrease in the average time of disappearance of horse serum from the blood of immunized rabbits in contrast to rabbits receiving horse serum for the first time. They did not observe the effect of large amounts of antiserum on the titer of horse serum which had been circulating for several days, nor did they observe the effect of large amounts of antiserum on serum sickness in rabbits. Not Longcope and Rackemann, Fleisher and Jones, nor MacKenzie and Fruhbauer offer any evidence that subsidence of symptoms correspond to the *disappearance* of horse serum. They do, however, present evidence that there is a relatively abrupt drop in horse serum titer and a corresponding rise in precipitin titer about the time symptoms subside. This seems to be the crux of the problem of the control of delayed reactions to serum. Theoretically, then, immediate serum reactions in man should be prevented by injecting enough specific antibody before injecting horse serum, and beginning serum sickness in man and rabbits should be aborted by injecting enough antibody to raise, abruptly, the anti-horse serum precipitin titer and lower the horse serum titer of the patient's blood.

Technical difficulties in demonstrating the presence of allergic antibodies in the tissues, and even in the blood, tend to vitiate the significance of the inability of Tuft and Ramsdell[10] to show a relationship between serum sickness and precipitin and horse serum titers in man. An apparent obstacle to the proof of the theory that serum sickness can be aborted by injecting specific antibody is the phenomenon of reversed anaphylaxis, i.e., the production of anaphylactic shock by injecting specific antiserum into an animal which has previously received antigen. Opie and Furth,[11] however, showed that these reactions could be avoided by desensitizing, in twelve to eighteen hours, with small doses of antiserum.

It is obvious that the specific control of human serum reactions with whole immune serum would not be feasible, because it would itself be more likely to produce reactions than the various refined therapeutic serums in use at present. Therefore, before using specific immune serum in the attempt to control human serum reactions, it should be

refined to the point of maximum antibody content per unit of reaction-producing substance.

In accordance with the above mentioned working hypothesis for the rational specific control of human serum reactions, experiments have been outlined which are intended to prove: (1) that the anaphylactic antibody can be refined; (2) that this refined anaphylactic antibody will protect highly sensitized guinea pigs from shocking doses of horse serum; (3) that this refined anaphylactic antibody will desensitize, and can then be given safely in large amounts to rabbits which have previously received horse serum; (4) that this refined antibody will or will not abort serum sickness in rabbits; (5) that this refined antibody will or will not abort serum sickness in man; (6) that this refined antibody will or will not prevent immediate serum reactions in man.

In this report it will be shown: (Part I) that the anaphylactic antibody can be refined, i.e., that guinea pigs can be passively sensitized with antibody precipitated with the globulin from immune serum; (Part II) that the anaphylactic antibody is widely distributed through the various globulin fractions; (Part III) that the refined antibody will protect highly sensitized guinea pigs against shocking doses of horse serum. Results of the experiments on serum reactions in rabbits and human beings and the methods of preparing antibody solutions for use in human beings will be reported when they are completed.

TECHNICAL DETAILS

Immune rabbit serum was used throughout as the source of antibody and to sensitize guinea pigs passively for the protection experiments. The rabbits were first immunized by intraperitoneal injections of 2 c.c. of horse serum three times a week for two weeks. They were bled from the heart on the thirteenth or fourteenth day after the sixth immunizing injection. In order to obtain serum every eighteen or nineteen days instead of once a month, another immunizing schedule of three intraperitoneal injections of 3 c.c. of horse serum on alternate days, then 1 c.c. subcutaneously after six days, then bleeding from the heart after six or seven days, was begun immediately. Serum so obtained was pooled. In every pooled sample the anti-horse serum precipitin titer was between 1:5,000 and 1:10,000.

Preparation of Antibody Solutions.—Pooled immune rabbit serum was diluted with an equal quantity of water and warmed to about 38° C. Anhydrous sodium sulphate, to make 20 per cent, was dissolved in it and allowed to stand in the incubator about an hour. The globulin thus precipitated was collected in the incubator by filtering the mixture through heavy paper and dialyzed in cellophane sacs against running water. The globulin in the sacs went into solution promptly at first, but in about twenty-four hours a heavy precipitate appeared. Up to this point the procedure is identical with Felton's technic[12] for the

preparation of pneumococcus antibody solutions. After about five days the sac contents were separated into the supernatant water-soluble (or pseudoglobulin) and the precipitated water-insoluble (or euglobulin) fractions by centrifugalization. The precipitate was dissolved in 0.9 per cent saline and designated *water-insoluble-antibody fraction.* The supernatant, with sodium chloride added to make 0.9 per cent, was designated *water-soluble-antibody solution.* In some of the protection experiments whole globulin from the dialyzing sac, with sodium chloride added to dissolve the precipitate, was used. This was designated *whole-globulin-antibody solution.*

Before injection into guinea pigs the solutions were passed through a Seitz bacterial filter.

In every instance the anti-horse serum precipitin titer of each of the three antibody solutions was about 1:5,000, and the volume of the dialyzing sac contents was about half of the original serum.

Protein nitrogen determinations of the various serum fractions, in milligrams per 100 c.c., prepared as in Experiment V, were as follows: whole immune serum, 1,087; whole-globulin-antibody solution, 267; water-soluble-antibody solution, 175; water-insoluble-antibody fraction, 196.

Control solutions were prepared from normal nonimmunized rabbit serum in exactly the same way. They will be called: *water-soluble-control solution, water-insoluble-control fraction,* and *whole-globulin-control solution.*

Test and Control Animals.—Guinea pigs were used throughout. The virgin females used in the Dale preparations weighed about 16 ounces, all others between 10 and 14 ounces.

Intravenous injections were by gravity through a rubber tube and No. 22 gauge needle leading from a syringe, the lower end of which was about six inches above the animal. The jugulars were exposed through a midline incision in the neck under novocaine anesthesia. Two 14 ounce guinea pigs were given 25 c.c. and 20 c.c., respectively, of normal saline in twelve minutes by this method without any detectable reaction. This was done to show that the mechanical effects of the injections were negligible.

Anaphylactic reactions were recorded as: fatal, convulsions but recovered, severe, moderate, slight transient, and no reaction. The severe, moderate and slight transient reactions were classified on the basis of the degree of expiratory dyspnea observed. The severe cases were nearly as dyspneic and sick as those with convulsions. The moderate cases were obviously but not alarmingly dyspneic. The slight transient cases had little more than borderline reactions.

Autopsies were done on most of the fatal cases. The combination of ballooned lungs with rounded borders and petechial hemorrhages, a dilated right heart with petechial hemorrhages was recorded as typical.

The autopsies were considered necessary to the diagnosis of anaphylactic death because in several animals not reported, and in No. 17 in Table II, the dyspnea and convulsions which preceded death were indistinguishable from the dyspnea and convulsions in immediate anaphylactic asphyxia. But autopsies of these animals showed them to have small contracted lungs and large bubbles of air in their pulmonary arteries and right ventricles. Microsections of the lungs of five animals showed the typical findings of Schultz and Jordan.[13] Those with air emboli did **not.**

PART I

The Anaphylactic Antibody Can Be Refined

As stated in the introduction, the first step in the problem of the rational specific control of human serum reactions was to demonstrate that the anaphylactic antibody can be refined. If guinea pigs could be passively sensitized with one of the antibody solutions described under technical details, it would prove that the anaphylactic antibody could be refined. Otto and others[14] and Doerr and Hallauer[15] passively sensitized a few guinea pigs with the two globulin fractions obtained from immune sera by electro-osmosis and ammonium sulphate precipitation. They did not agree, however, upon the distribution of the antibody between the globulin fractions. This will be referred to again in Part II.

The following experiments were designed to show that guinea pigs can be passively sensitized with the antibody solution given either intraperitoneally or intravenously. The presence of passive sensitization is to be shown by anaphylactic reactions to intravenous injections of horse serum and by the Dale[16] method of demonstrating specific hypersensitiveness in the excised uterus of virgin female guinea pigs.

The water-soluble-antibody solution was used arbitrarily in this group of experiments. The amounts and numbers of sensitizing injections of antibody solution, and the interval between sensitizing and shocking injections of horse serum were also arbitrarily chosen.

Experiment I (Table I).—Guinea pigs can be passively sensitized by intraperitoneal injections of antibody solutions and shocked by intravenous injections of horse serum.

Eleven test guinea pigs were given daily intraperitoneal injections of 2 c.c. or 3 c.c. of antibody solution for three days. The next day each animal was given a shocking dose of 2 c.c. of horse serum intravenously. Seven of the eleven died of anaphylactic shock within three minutes, two had convulsions but recovered, two had moderate dyspnea. In other words, all had typical anaphylactic shock of varying degree. Autopsy findings in the seven which died were typical of anaphylaxis.

Twelve control pigs treated identically with water-soluble control solution did not react at all to injections of 2.5 c.c. of horse serum.

TABLE I

TEST	SENSITIZING DATA									SHOCKING DATA							
														REACTION			AUTOPSY
G P	ROUTE	MATERIAL	DATE	AMOUNT	DATE	AMOUNT	DATE	AMOUNT	REACTION	ROUTE	MATERIAL	DATE	AMOUNT	PRESENT	FATAL	RECOVERED	TYPICAL
1	IP	Antibody Sol.	11/28	2 c.c.	11/29	2 c.c.	11/30	3 c.c.	0	IV	HS	12/1	2 c.c.	+	+		+
2	IP	Antibody Sol.	11/28	2 c.c.	11/29	2 c.c.	11/30	3 c.c.	0	IV	HS	12/1	2 c.c.	+	+		+
3	IP	Antibody Sol.	11/28	2 c.c.	11/29	2 c.c.	11/30	3 c.c.	0	IV	HS	12/1	2 c.c.	+	+		+
4	IP	Antibody Sol.	11/28	2 c.c.	11/29	2 c.c.	11/30	3 c.c.	0	IV	HS	12/1	2 c.c.	±		+	
5	IP	Antibody Sol.	11/28	2 c.c.	11/29	2 c.c.	11/30	3 c.c.	0	IV	HS	12/1	2 c.c.	±		+	
6	IP	Antibody Sol.	11/28	2 c.c.	11/29	2 c.c.	11/30	3 c.c.	0	IV	HS	12/1	2 c.c.	+		+	
7	IP	Antibody Sol.	12/ 1	2 c.c.	12/ 2	2 c.c.	12/ 3	3 c.c.	0	IV	HS	12/4	2 c.c.	+	+		+
8	IP	Antibody Sol.	12/ 1	2 c.c.	12/ 2	2 c.c.	12/ 3	3 c.c.	0	IV	HS	12/4	2 c.c.	+	+		+
9	IP	Antibody Sol.	12/ 1	2 c.c.	12/ 2	2 c.c.	12/ 3	3 c.c.	0	IV	HS	12/4	2 c.c.	+	+		+
10	IP	Antibody Sol.	12/ 1	2 c.c.	12/ 2	2 c.c.	12/ 3	3 c.c.	0	IV	HS	12/4	2 c.c.	+	+		+
11	IP	Antibody Sol.	12/ 1	2 c.c.	12/ 2	2 c.c.	12/ 3	3 c.c.	0	IV	HS	12/4	2 c.c.	+		+	
													Total	11	7	4	7
CONTROL																	
1	IP	Control Solution	12/ 2	2 c.c.	12/ 3	2 c.c.	12/ 4	3 c.c.	0	IV	HS	12/5	2.5 c.c.	0			
2	IP	Control Solution	12/ 2	2 c.c.	12/ 3	2 c.c.	12/ 4	3 c.c.	0	IV	HS	12/5	2.5 c.c.	0			
3	IP	Control Solution	12/ 2	2 c.c.	12/ 3	2 c.c.	12/ 4	3 c.c.	0	IV	HS	12/5	2.5 c.c.	0			
4	IP	Control Solution	12/ 2	2 c.c.	12/ 3	2 c.c.	12/ 4	3 c.c.	0	IV	HS	12/5	2.5 c.c.	0			
5	IP	Control Solution	12/ 2	2 c.c.	12/ 3	2 c.c.	12/ 4	3 c.c.	0	IV	HS	12/5	2.5 c.c.	0			
6	IP	Control Solution	12/ 2	2 c.c.	12/ 3	2 c.c.	12/ 4	3 c.c.	0	IV	HS	12/5	2.5 c.c.	0			
7	IP	Control Solution	12/ 3	2 c.c.	12/ 4	2 c.c.	12/ 5	3 c.c.	0	IV	HS	12/7	2.5 c.c.	0			
8	IP	Control Solution	12/ 3	2 c.c.	12/ 4	2 c.c.	12/ 5	3 c.c.	0	IV	HS	12/7	2.5 c.c.	0			
9	IP	Control Solution	12/ 3	2 c.c.	12/ 4	2 c.c.	12/ 5	3 c.c.	0	IV	HS	12/7	2.5 c.c.	0			
10	IP	Control Solution	12/ 3	2 c.c.	12/ 4	2 c.c.	12/ 5	3 c.c.	0	IV	HS	12/7	2.5 c.c.	0			
11	IP	Control Solution	12/ 3	2 c.c.	12/ 4	2 c.c.	12/ 5	3 c.c.	0	IV	HS	12/7	2.5 c.c.	0			
12	IP	Control Solution	12/ 3	2 c.c.	12/ 4	2 c.c.	12/ 5	3 c.c.	0	IV	HS	12/7	2.5 c.c.	0			
													Total	0			

IP = intraperitoneal, IV = intravenous, HS = horse serum.

TABLE II

TEST	SENSITIZING DATA					SHOCKING DATA								
										REACTION			AUTOPSY	
G P	ROUTE	MATERIAL	DATE	AMOUNT C.C.	REACTION	ROUTE	MATERIAL	DATE	AMOUNT C.C.	PRESENT	FATAL	RECOVERED	TYPICAL	ATYPICAL
1	IV	Antibody Sol.	7/30	5	0	IV	HS	8/ 3	2.0	+	+			
2	IV	Antibody Sol.	8/ 8	5	0	IV	HS	8/11	2.0	+		+		
3	IV	Antibody Sol.	8/ 8	5	0	IV	HS	8/11	2.0	+		+		
4	IV	Antibody Sol.	8/ 9	4	0	IV	HS	8/11	2.5	0				
5	IV	Antibody Sol.	8/ 9	4	0	IV	HS	8/11	2.0	0				
6	IV	Antibody Sol.	8/ 9	4	0	IV	HS	8/11	2.0	0				
7	IV	Antibody Sol.	8/ 9	4	0	IV	HS	8/11	2.0	0				
8	IV	Antibody Sol.	8/15	5	0	IV	HS	8/22	2.0	0				
9	IV	Antibody Sol.	8/15	5	0	IV	HS	8/22	2.0	0				
10	IV	Antibody Sol.	8/15	5	0	IV	HS	8/22	2.0	0				
11	IV	Antibody Sol.	8/15	5	±	IV	HS	8/22	1.75	+	+		+	
12	IV	Antibody Sol.	8/16	5	0	IV	HS	8/22	1.2	+	+		+	
13	IV	Antibody Sol.	8/16	5	0	IV	HS	8/22	0.6	+	+		+	
14	IV	Antibody Sol.	9/ 6	5	0	IV	HS	9/12	1.9	+	+		+	
15	IV	Antibody Sol.	9/ 6	5	0	IV	HS	9/12	2.0	+	+		+	
16	IV	Antibody Sol.	9/ 6	5	0	IV	HS	9/12	1.8	+	+		+	
17	IV	Antibody Sol.	9/ 6	5	0	IV	HS	9/12	2.0	+*	+*		0	Air embolism
18	IV	Antibody Sol.	9/ 6	4	0	IV	HS	9/12	2.5	+*	+*		0	Lung collapsed
19	IV	Antibody Sol.	9/ 6	5	0	IV	HS	9/12	2.5	+		+		
20	IV	Antibody Sol.	9/15	5	0	IV	HS	9/21	2.4	0				
21	IV	Antibody Sol.	9/15	5	0	IV	HS	9/21	1.7	+	+		+	
22	IV	Antibody Sol.	9/15	5	0	IV	HS	9/21	2.0	0				
23	IV	Antibody Sol.	9/15	5	0	IV	HS	9/21	4.0	0				
24	IV	Antibody Sol.	9/15	5	0	IV	HS	9/21	2.5	+		+		
25	IV	Antibody Sol.	9/15	5	0	IV	HS	9/21	2.5	+	+		+	
									Total	13	9	4	8	2

TABLE II—CONT'D

CONTROL	SENSITIZING DATA					SHOCKING DATA							
										REACTION		AUTOPSY	
G P	ROUTE	MATERIAL	DATE	AMOUNT C.C.	REACTION	ROUTE	MATERIAL	DATE	AMOUNT C.C.	PRESENT	FATAL	TYPICAL	ATYPICAL
1	IV	Control Solution	8/ 8	2.5	0	IV	HS	8/11	2.5	0			
2	IV	Control Solution	8/ 8	5.0	0	IP	HS	8/11	2.0	0			
3	IV	Control Solution	8/ 9	4.0	0	IV	HS	8/11	2.5	0			
4	IV	Control Solution	8/ 9	4.0	0	IV	HS	8/11	2.5	0			
5	IV	Control Solution	8/23	5.0	0	IV	HS	8/30	2.5	0			
6	IV	Control Solution	8/23	5.0	0	IV	HS	8/30	2.5	0			
7	IV	Control Solution	8/23	5.0	0	IV	HS	8/30	2.5	0			
8	IV	Control Solution	9/14	5.0	0	IV	HS	9/20	2.5	0			
9	IV	Control Solution	9/14	5.0	0	IV	HS	9/20	2.5	0			
10	IV	Control Solution	9/14	5.0	0	IV	HS	9/20	2.0	0			
11	IV	Control Solution	9/14	5.0	0	IV	HS	9/20	2.5	0			
12	IV	Control Solution	9/14	5.0	0	IV	HS	9/20	2.5	0			
13	IV	Control Solution	9/14	5.0	0	IV	HS	9/20	2.5	0			
14	IV	Control Solution	9/14	5.0	0	IV	HS	9/20	2.5	0			
15	IV	Control Solution	11/ 4	5.0	0	IV	HS	11/ 9	2.5	+	+	±	
16	IV	Control Solution	11/ 4	5.0	0	IV	HS	11/ 9	2.5	0			
17	IV	Control Solution	11/ 4	5.0	0	IV	HS	11/ 9	2.5	0			
18	IV	Control Solution	11/ 4	5.0	0	IV	HS	11/ 9	2.5	0			
19	IV	Control Solution	11/ 4	5.0	0	IV	HS	11/ 9	2.5	0			
20	IV	Control Solution	11/ 4	5.0	0	IV	HS	11/ 9	2.5	0			
21	IV	Control Solution	11/ 4	5.0	0	IV	HS	11/ 9	2.5	0			
22	IV	Control Solution	11/ 4	5.0	0	IV	HS	11/ 9	2.5	0			
23.	IV	Control Solution	11/ 4	5.0	0	IV	HS	11/ 9	2.5	0			
24	IV	Control Solution	11/ 5	4.0	0	IV	HS	11/10	2.5	0			
25	IV	Control Solution	11/ 5	4.0	0	IV	HS	11/10	2.5	0			
26	IV	Control Solution	11/ 5	4.0	0	IV	HS	11/10	2.5	0			
									Total	1	1		

Experiment II (Table II).—Guinea pigs can be passively sensitized by intravenous injections of antibody solution and shocked by intravenous injections of horse serum.

Twenty-five test guinea pigs were given one sensitizing intravenous injection of 4 c.c. or 5 c.c. of antibody solution. One animal was sick after the sensitizing dose but did not have symptoms of anaphylaxis. Two to seven days later each was given a shocking dose of 0.6 to 4.0 c.c. of horse serum. Eleven of the 25 died almost immediately in what seemed to be anaphylactic shock. Four had moderate dyspnea. Ten did not react. Eight of the 11 fatal cases had typical anaphylactic findings when autopsied. One was not autopsied. Another (No. 17) had small lungs and large air bubbles in the pulmonary artery and right ventricle. The other (No. 18) had collapsed lungs with all the other signs of anaphylaxis and no emboli. These last two are not included in the total number of fatal anaphylactic reactions in Table II.

Twenty-five of the 26 control animals, which were given water-soluble-control solution, instead of the antibody solution, did not react to 2 c.c. or more of horse serum. One of the control animals died in convulsions while the horse serum was being given. When autopsied the lungs were not ballooned or collapsed or hemorrhagic. No emboli were found. The right heart was dilated. No attempt is made to explain this death. One animal, not reported, died similarly while being tied to the operating board.

In summary, 13 of 25 test animals were sensitized by one intravenous injection of antibody solution while 25 of 26 controls were not sensitized.

Experiment III (Table III).—The guinea pig uterus can be sensitized by the antibody solution.

Four virgin female guinea pigs were given from two to five intraperitoneal and intravenous sensitizing injections of 2 c.c. to 4 c.c. of antibody solution. The day after the last sensitizing injection the excised uterine horns were transferred to a 125 c.c. Ringer's bath at 38° to 40° C. Each horn, in turn, was then mounted in a simple Ringer's bath-uterine horn-heart lever-kymograph preparation as described by Dale.[16] After a preliminary tracing, 1 c.c. of guinea pig or dog serum was added to the bath and later 1 c.c. of horse serum. The effects were recorded graphically.

The excised uterine horns from three control animals, prepared with water-soluble-control solution instead of the antibody solution, were similarly tested with guinea pig, or dog, and horse serum. The horse serum was tested for toxicity by adding it in high concentration to a strip of cat intestine similarly mounted. No effect was noted.

The results are tabulated in Table III and photographed in Figs. 1 and 2.

TABLE III

SENSITIZING DATA

	TEST				CONTROL		
G P	1	2	3	4	5	6	7
Material	Antibody Sol.	Antibody Sol.	Antibody Sol.	Antibody Sol.	Control Solution	Control Solution	Control Solution
Date	11/14	11/14	11/14	11/26	12/10	12/10	12/10
Amount	2 c.c.	2 c.c.	2 c.c.	2 c.c.	2 c.c.	2 c.c.	2 c.c.
Route	IP	IP	IP	IP	IP	IP	IP
Date	11/15	11/15	11/15	11/27	12/11	12/11	12/11
Amount	3 c.c.	3 c.c.	3 c.c.	2 c.c.	2 c.c.	2 c.c.	2 c.c.
Route	IV	IV	IV	IP	IP	IP	IP
Date		11/18	11/18	11/28	12/12	12/12	12/12
Amount		2 c.c.	2 c.c.	4 c.c.	3 c.c.	3 c.c.	3 c.c.
Route		IP	IP	IV	IV	IV	IV
Date		11/19	11/19				
Amount		2 c.c.	2 c.c.				
Route		IP	IP				
Date		11/20	11/20				
Amount		3 c.c.	3 c.c.				
Route		IP	IP				
Reaction	0	0	0	0	0	0	0

SHOCKING DATA

Date	11/16	11/21	11/21	11/29	12/13	12/13	12/13
Shock Tissue	Uterus	Uterus	Uterus	Uterus	Uterus	Uterus	Uterus
Horn I.							
Reaction		GPS	GPS	DS		DS	DS
Material		0	0	0		0	0
Material	HS	HS	HS	HS	HS	HS	HS
Reaction	+	+	+	+	0	0	0
Horn II.							
Material	GPS		GPS	DS			
Reaction	0		0	0			
Material	HS	HS	HS	HS			HS
Reaction	+	0	0	+			0

GPS = guinea pig serum.
DS = Dog serum.

In summary: Excised uterine horns from animals sensitized by the antibody solution contracted when exposed to horse serum. They did not contract when exposed to dog serum or to guinea pig serum. Excised horns from control animals did not react to horse serum, guinea pig serum or dog serum.

PART II

The Anaphylactic Antibody Is Widely, But Not Equally, Distributed Among a Number of Different Globulin Fractions

In Part I it was shown that at least a part of the anaphylactic antibody can be refined to the water-soluble fraction of the globulin precipitated from anti-horse rabbit serum by 20 per cent sodium sulphate. As a preliminary to the more complicated problem of quantitative re-

finement, it seemed important to study qualitatively the distribution of the anaphylactic antibody between the various globulin fractions. Doerr and Hallauer[15] seemed to show that the antibody was present in both the euglobulin (water-insoluble) and the pseudoglobulin (water-

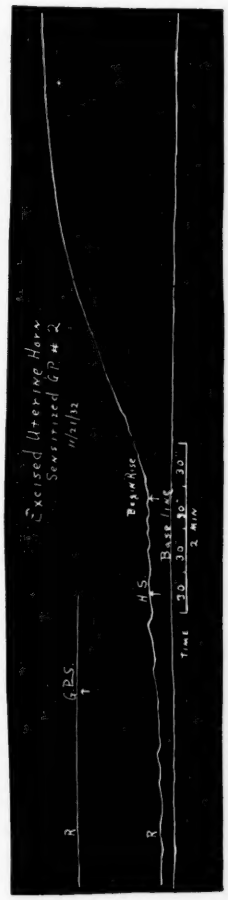

Fig. 1.

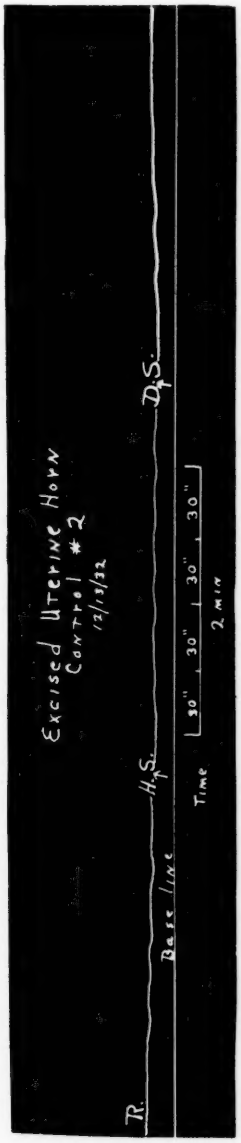

Fig. 2.

soluble) fractions. Otto and Shirakawa[14] at first claimed that the antibody was present only in the pseudoglobulin fraction, while the precipitin was present only in the euglobulin. Later Otto and Iwanoff[14] claimed to have found (in seemingly identical experiments) the anaphylactic anti-

body and precipitin together in first the pseudoglobulin and then the euglobulin fractions. Both groups of investigators separated the immune serum into albumin, pseudoglobulin, and euglobulin fractions by electro-osmosis and half-saturation with ammonium sulphate. The present group of experiments was devised to show, first, the presence or absence of the anaphylactic antibody and precipitin in carefully purified albumin, water-soluble, and water-insoluble-antibody fractions; and second, the presence of the antibody and precipitin in the fractions precipitated serially from dilute whole-globulin-antibody solutions by increasing concentrations of sodium sulphate.

Experiment IV (Table IV).—Albumin fractions of anti-horse immune rabbit serum do not contain precipitin, but the water-soluble and the water-insoluble-antibody fractions contain both precipitin and the anaphylactic antibody.

TABLE IV

G P	SENSITIZING SOLUTION	SHOCKING DOSE H S	REACTION	PRECIPITIN TITER OF SENSITIZING SOLUTION
1	5 c.c. water soluble antibody	1.5 c.c.	Fatal	1:5000
2	4.5 c.c. water insoluble antibody	2.4 c.c.	Fatal	1:5000
3	4.5 c.c. water insoluble antibody	2.3 c.c.	Fatal	1:5000
–	Albumin	------	–	0

Anti-horse rabbit serum with a precipitin titer of over 1:5,000 was precipitated with 20 per cent sodium sulphate and filtered as previously described.

The filtrate containing the albumin was precipitated by saturation with ammonium sulphate. Half saturation with ammonium sulphate then produced no precipitate, indicating that globulin precipitation was complete. The precipitated albumin was dialyzed four days against running water, filtered and tested for precipitin.

The precipitated globulin was dissolved in physiologic salt solution and made up to three times the original volume, reprecipitated with 20 per cent sodium sulphate, and filtered. The second precipitation was done to get rid of the remaining traces of albumin. The second filtrate was discarded. The precipitate was dialyzed four days against running water, then thirty-six hours against distilled water.

The contents of the dialyzing sac were centrifuged The supernatant, containing water-soluble globulin, was filtered through heavy filter paper. The precipitate was washed three times with twice the original serum volume of distilled water. The supernatants from each washing were added to the supernatant from the dialyzing sac, and the mixture was allowed to stand in the ice box overnight. In the

morning no precipitate had formed. The water-soluble globulin in the combined supernatants was then precipitated as usual with sodium sulphate and filtered. This precipitate was dialyzed four days against running water, sodium chloride added to make 0.9 per cent, filtered for sterility, tested for precipitin, and 3 c.c. injected into a guinea pig. This was called *purified-water-soluble-antibody solution.* The thrice-washed precipitate from the first dialyzing sac was dissolved in physiologic salt solution and made up to three times the original volume, filtered, reprecipitated with 20 per cent sodium sulphate, filtered, the precipitate dialyzed, dissolved in physiologic saline solution, filtered for sterility, tested for precipitin, and 4.5 c.c. were injected into each of two guinea pigs, in exactly the same manner as the supernatant. This was called *purified-water-insoluble-antibody fraction.* The following day the three guinea pigs were injected with horse serum. The results of this experiment were: The albumin fraction gave a negative precipitin test; both antibody fractions had a precipitin titer of 1:5,000; the guinea pigs sensitized with the antibody fractions had fatal reactions to the horse serum injections.

Experiment V (Table V).—Albumin fractions of anti-horse immune rabbit serum do not contain precipitin nor anaphylactic antibody; but both antibody fractions, less carefully prepared than in Experiment IV, contain precipitin and the anaphylactic antibody.

TABLE V

G P	SENSITIZING SOLUTION	SHOCKING DOSE H S	REACTION	PRECIPITIN TITER OF SENSITIZING SOLUTION
1	5 c.c. water soluble antibody	2.5 c.c.	Convulsions	1:4000+
2	5 c.c. water soluble antibody	2.5 c.c.	Fatal	--
3	5 c.c. water soluble antibody	2.5 c.c.	Fatal	--
4	5 c.c. water insoluble antibody	2.5 c.c.	Sl. dyspnea	1:1000+
5	5 c.c. water insoluble antibody	2.5 c.c.	Fatal	--
6	5 c.c. water insoluble antibody	2.5 c.c.	Fatal	--
7	5 c.c. albumin	2.5 c.c.	None	Negative
8	5 c.c. albumin	2.5 c.c.	None	--
9	5 c.c. albumin	2.5 c.c.	None	--
10	None (control)	2.5 c.c.	None	--
11	None (control)	2.5 c.c.	None	--

Globulin was precipitated by 20 per cent sodium sulphate, filtered, suspended in water, reprecipitated, filtered and dialyzed. The first filtrate, containing the albumin, was treated as in Experiment IV, and in addition 5 c.c. were injected into each of three guinea pigs. The contents of the dialyzing sac were centrifuged. The supernatant after centrifugalization at high speed for thirty minutes was filtered for sterility, tested for precipitin, and 5 c.c. were injected into each of three guinea pigs. This was called refined-water-soluble-antibody solu-

tion. The precipitate after centrifugalization was dissolved in a volume of physiologic saline solution equal to the supernatant, filtered for sterility, tested for precipitin, and 5 c.c. were injected into each of three guinea pigs. This was called refined-water-insoluble-antibody solution. The following day these nine guinea pigs were injected with horse serum. Two untreated ones were used as controls. The results of this experiment were: The albumin contained neither precipitin nor the anaphylactic antibody. Both antibody solutions contained both precipitin and anaphylactic antibodies. The controls did not react to horse serum.

Experiments IV and V seem to show qualitatively that the sensitizing or anaphylactic antibody and precipitin are abundantly present in both the water-soluble and the water-insoluble-antibody fractions. No evidence of either antibody could be found in the albumin. This is consistent with the findings of Doerr and Hallauer.[15]

Experiment VI (Table VI).—The anaphylactic antibody is widely but not equally distributed among the different globulin fractions precipitated serially by increasing amounts of sodium sulphate.

TABLE VI

PRECIPITATE FROM SOD. SULPH. %	AMOUNT SOLUTION FORMED	PRECIPITIN TITER 1:10	1:100	1:1000	G P	SENSITIZING DOSE	SHOCKING DOSE H S	REACTION
7.5	11.0 c.c.	4+	2+	1+	1	1.5 c.c.	3.0 c.c.	Convulsions
10.0	38 c.c.	4+	4+	4+	2	5.0 c.c.	1.9 c.c.	Fatal
12.5	2.5 c.c.	4+	4+	2+	3	2.5 c.c.	1.6 c.c.	Fatal
15.0	10.0 c.c.	4+	2+	1+	4	5.0 c.c.	1.8 c.c.	Fatal
15.0	–	4+	2+	1+	5	5.0 c.c.	2.0 c.c.	Fatal
17.5	8.0 c.c.	4+	1+	1+	6	4.0 c.c.	2.0 c.c.	Fatal
17.5	–	4+	1+	1+	7	4.0 c.c.	2.0 c.c.	Fatal
20.0	2.5 c.c.	1+	±	±	8	2.5 c.c.	2.5 c.c.	Sl. trans. dyspnea
22.5	2.5 c.c.	1+	±	±	9	2.5 c.c.	2.5 c.c.	Sl. trans. dyspnea

Sodium sulphate to make 5 per cent was added to a measured quantity of whole-globulin-antibody solution prepared as described in the section on technical details. No precipitate was formed. When sodium sulphate was added to make 7.5 per cent, a precipitate was formed. This precipitate was removed by filtration, dialyzed against running water, sodium chloride added to make 0.9 per cent, filtered for sterility, tested for precipitin and injected into a guinea pig.

The filtrate from the 7.5 per cent precipitation was made up to the original volume and sodium sulphate added to make 10 per cent. The resulting precipitate was treated like the 7.5 per cent precipitate. This same process was repeated with precipitates and filtrates formed by serial concentrations of 12.5 per cent, 15 per cent, 17.5 per cent, 20 per cent, and 22.5 per cent sodium suphate. All precipitations and

filtrations were done in the incubator to prevent crystallization, especially in the higher concentrations. The saline solutions of these precipitates after dialysis were designated as 7.5 per cent, 10 per cent, etc., solutions and were injected into guinea pigs as sensitizing doses of antibody. The next day the pigs were injected with shocking doses of horse serum.

No precipitates were formed by sodium sulphate concentrations below about 7.5 per cent nor above 22.5 per cent. Though precipitin and the anaphylactic antibody were demonstrable in all of the precipitates, only relatively small amounts were precipitated at 7.5 per cent, 12.5 per cent, 20 per cent, and 22.5 per cent. The amount of 7.5 per cent precipitate from two other antibody solutions, not tabulated, was too small to be recovered. Precipitates from all other concentrations were comparable. More detailed quantitative studies of the precipitates below 10 per cent and above 17.5 per cent will be made later. The data presented are sufficient to show qualitatively that the anaphylactic antibody is widely but not equally distributed among the globulin fractions precipitable by serial concentrations of sodium sulphate.

PART III

Highly Sensitized Guinea Pigs Can Be Protected Against Shocking Doses of Horse Serum by Crudely Refined Antibody

It was stated in the introduction that the second step in the problem of the rational specific control of human serum reactions was to demonstrate that refined antibody solutions could protect sensitized guinea pigs against shocking doses of horse serum. Reference was made to Weil's[4] experiments in which he protected highly sensitized guinea pigs against from five to ten times the shocking dose of horse serum by first injecting 1.5 c.c. to 3.5 c.c. of whole serum from rabbits highly immunized against horse serum. He emphasized the fact that the protecting dose of immune serum represented fifteen to thirty times the sensitizing dose of the same serum. In this problem the important facts are whether antibody solutions will protect sensitized guinea pigs from shocking doses of horse serum and whether the antibody can be sufficiently concentrated and refined to be used freely in human beings. The number of sensitizing doses of immune serum needed to protect is irrelevant. The further concentration and refinement of the antibody will be studied later. The following experiments were designed to show that the water-soluble-antibody solution and the whole-globulin-antibody solution are capable of protecting guinea pigs against shocking doses of horse serum. By shocking dose is meant that amount of horse serum which uniformly produces severe dyspnea, convulsions or anaphylactic death in highly sensitized guinea pigs. The test and control animals in these experiments were sensi-

tized passively by intraperitoneal injections of 2 c.c. to 3 c.c. of anti-horse rabbit serum with a precipitin titer of about 1:7,500. The protection and control experiments were done twenty-four to thirty-six hours after the sensitizing injections. The horse serum was diluted 1:40 with 0.9 per cent sodium chloride to facilitate measurement of the shocking doses.

Experiment VII (Table VII).—The water-soluble-antibody solution can protect against shocking doses of horse serum.

TABLE VII

POSITIVE CONTROLS

DATE	G P	AMOUNT H S	REACTION
3/2	1	0.025 c.c.	Convulsions
	2	0.025 c.c.	Fatal
	3	0.0125 c.c.	Moderate dyspnea
3/3	4	0.0125 c.c.	Slight dyspnea
	5	0.025 c.c.	Fatal
	6	0.025 c.c.	Fatal
	7	0.025 c.c.	Convulsions
3/9	8	0.025 c.c.	Severe dyspnea
	9	0.025 c.c.	Severe dyspnea
	10	0.025 c.c.	Severe dyspnea
	11	0.025 c.c.	None

TEST

DATE	G P	ANTIBODY SOLUTION	INTERVAL	AMOUNT H S	REACTION	PROTECTION
3/2	12	5 c.c.	3 to 5 min.	0.0375 c.c.	Convulsions	None
	13	6 c.c.	3 to 5 min.	0.025 c.c.	Fatal	None
	14	6 c.c.	3 to 5 min.	0.025 c.c.	Mod. dyspnea	Partial
	15	6 c.c.	3 to 5 min.	0.025 c.c.	Mod. dyspnea	Partial
3/3	16	6 c.c.	3 to 5 min.	0.025 c.c.	Mod. dyspnea	Partial
	17	6 c.c.	3 to 5 min.	0.025 c.c.	None	Complete
	18	6 c.c.	3 to 5 min.	0.025 c.c.	Sl. trans. dyspnea	Almost complete
3/9	19	6 c.c.	3 to 5 min.	0.025 c.c.	Sl. trans. dyspnea	Almost complete
	20	6 c.c.	3 to 5 min.	0.025 c.c.	Sl. trans. dyspnea	Almost complete
	21	6 c.c.	3 to 5 min.	0.025 c.c.	None	Complete
	22	6 c.c.	3 to 5 min.	0.025 c.c.	None	Complete

Eleven control and 11 test guinea pigs which had been highly sensitized were used on three different days. The control animals were injected intravenously with 0.0125 c.c. to 0.025 c.c. of horse serum. All but one of the nine which received 0.025 c.c. of horse serum had severe dyspnea, convulsions or anaphylactic death. The two receiving 0.0125 c.c. of horse serum had moderate or slight dyspnea. All but one of the test animals received 6 c.c. of water-soluble-antibody solution intravenously about five minutes before receiving 0.025 c.c. of horse serum. One of these died in anaphylactic shock, three had dyspnea of about the same degree as the controls which got 0.0125 c.c. of horse serum, three had slight transient, almost negligible, dyspnea, and three had no reaction whatever. The first test animal received

only 5 c.c. of antibody and 0.0375 c.c. of horse serum. This one had a convulsion but recovered.

Summary: By comparing test and control animals done on the same day it will be seen that the antibody solution definitely protected nine of ten test animals, partially or completely, against a shocking dose of horse serum.

Experiment VIII (Table VIII).—The water-soluble-antibody solution will protect against shocking doses of horse serum, but the water-soluble-control solution will not protect.

TABLE VIII

NEGATIVE CONTROLS

DATE	G P	CONTROL SOLUTION	INTERVAL	AMOUNT H S	REACTION	PROTECTION	PREDETERMINED M.S.D.*
	1	6 c.c.	5 min.	0.0375 c.c.	Fatal	None	0.0375 c.c.
3/24	2	6 c.c.	5 min.	0.0375 c.c.	Fatal	None	0.0375 c.c.
	3	6 c.c.	5 min.	0.0375 c.c.	Severe dyspnea	None	0.0375 c.c.
	4	6 c.c.	5 min.	0.05 c.c.	Fatal	None	0.05 c.c.
	5	6 c.c.	5 min.	0.05 c.c.	Fatal	None	0.05 c.c.
	6	6 c.c.	5 min.	0.05 c.c.	Fatal	None	0.05 c.c.
3/28	7	6 c.c.	5 min.	0.05 c.c.	Convulsions	None	0.05 c.c.
	8	6 c.c.	5 min.	0.05 c.c.	Severe dyspnea	None	0.05 c.c.
	9	6 c.c.	5 min.	0.05 c.c.	Severe dyspnea	None	0.05 c.c.
	10	6 c.c.	5 min.	0.05 c.c.	Moderate dyspnea	None	0.05 c.c.
				TEST			
		ANTIBODY SOLUTION					
	11	6 c.c.	5 min.	0.05 c.c.	Moderate dyspnea	Partial	0.0375 c.c.
3/24	12	6 c.c.	5 min.	0.05 c.c.	None	Complete	0.0375 c.c.
	13	6 c.c.	5 min.	0.05 c.c.	None	Complete	0.0375 c.c.
	14	6 c.c.	5 min.	0.05 c.c.	Fatal	None	0.05 c.c.
	15	6 c.c.	5 min.	0.05 c.c.	Sl. trans. dyspnea	Partial	0.05 c.c.
	16	6 c.c.	5 min.	0.05 c.c.	Sl. trans. dyspnea	Partial	0.05 c.c.
3/28	17	6 c.c.	5 min.	0.05 c.c.	Sl. trans. dyspnea	Partial	0.05 c.c.
	18	6 c.c.	5 min.	0.05 c.c.	Sl. trans. dyspnea	Partial	0.05 c.c.
	19	6 c.c.	5 min.	0.05 c.c.	None	Complete	0.05 c.c.
	20	6 c.c.	5 min.	0.05 c.c.	None	Complete	0.05 c.c.

*M.S.D. = Minimal shocking dose.

Ten control and 10 test guinea pigs which had been highly sensitized were used on two different days. A shocking dose of about 0.0375 c.c. and 0.05 c.c. of horse serum had been predetermined for the first and second sets of animals, respectively. The control animals were given 6 c.c. of water-soluble-control solution about five minutes before being given shocking doses of 0.0375 c.c. or 0.05 c.c. of horse serum. Nine of the ten had severe dyspnea, convulsions, or anaphylactic death. The other had moderate dyspnea. The test animals were treated identically except that water-soluble-antibody solution was used instead of the control solution. One of these had a fatal shock, another had moderate dyspnea. The rest had negligible or no reactions to the horse serum.

Summary: By comparing test and control animals done on the same day it will be seen that the antibody solution partially or completely protected 9 of the 10 test animals against a shocking dose of horse serum. The water-soluble-control solution did not protect.

Experiment IX (Table IX).—The whole-globulin-antibody solution will protect against shocking doses of horse serum more completely than the water-soluble-antibody solution and the whole-globulin-control solution will not protect.

TABLE IX

NEGATIVE CONTROLS

DATE	G P	CONTROL SOLUTION	INTERVAL	AMOUNT H S	REACTION	PROTECTION	PREDETERMINED M.S.D.*
5/2	1	6 c.c.	5 min.	0.0375 c.c.	Fatal	None	0.025 c.c.
	2	6 c.c.	5 min.	0.0375 c.c.	Fatal	None	0.025 c.c.
	3	6 c.c.	5 min.	0.0375 c.c.	Severe dyspnea	None	0.025 c.c.
	4	6 c.c.	5 min.	0.025 c.c.	Convulsions	None	0.025 c.c.
5/4	5	7 c.c.	5 min.	0.025 c.c.	Fatal	None	0.025 c.c.
	6	7 c.c.	5 min.	0.025 c.c.	Fatal	None	0.025 c.c.
	7	7 c.c.	5 min.	0.025 c.c.	Severe dyspnea	None	0.025 c.c.

TEST

		ANTIBODY SOLUTION					
5/2	8	6 c.c.	5 min.	0.0375 c.c.	None	Complete	0.025 c.c.
	9	6 c.c.	5 min.	0.0375 c.c.	Sl. trans. dysp.	Partial	0.025 c.c.
	10	6 c.c.	5 min.	0.0375 c.c.	None	Complete	0.025 c.c.
	11	6 c.c.	5 min.	0.0375 c.c.	None	Complete	0.025 c.c.
	12	6 c.c.	5 min.	0.075 c.c.	None	Complete	0.025 c.c.
5/4	13	7 c.c.	5 min.	0.0375 c.c.	None	Complete	0.025 c.c.
	14	7 c.c.	5 min.	0.05 c.c.	None	Complete	0.025 c.c.
	15	7 c.c.	5 min.	0.05 c.c.	None	Complete	0.025 c.c.

*M.S.D. = Minimal shocking dose.

Fifteen highly sensitized guinea pigs were used on two different days. It was determined previously that the shocking dose was about 0.025 c.c. of horse serum intravenously. Seven control animals received 6 c.c. or 7 c.c. of whole-globulin-control solution about five minutes before being given shocking doses of horse serum. Each of them had severe dyspnea, convulsions, or died.

Eight test animals received 6 c.c. or 7 c.c. of whole-globulin-antibody solution five minutes before being given 0.0375 c.c., 0.05 c.c., or 0.075 c.c. of horse serum. Only one of them had any reaction. This one had slight, transient, negligible dyspnea.

Summary: By comparing test and control animals done on the same day it will be seen that three were protected against two, one against one and a half, and three against single shocking doses of horse serum. The whole-globulin-control solution did not protect. In each experi-

ment all of the animals which died were autopsied. Each showed typical anaphylactic changes.

SUMMARY

It has been shown qualitatively that:

1. Guinea pigs can be passively sensitized to horse serum by injecting antibody solutions prepared from the pooled serum of rabbits highly immunized against horse serum.

2. The anaphylactic antibody was present in both the water-soluble and the water-insoluble globulin fractions of the immune serum.

3. The anaphylactic antibody was serially precipitated from sodium chloride suspensions of whole globulin by sodium sulphate in concentrations of 7.5 per cent, 10 per cent, 12.5 per cent, 15 per cent, 17.5 per cent, 20 per cent, 22.5 per cent. Precipitates from the various concentrations were not uniform in amount nor in precipitin titer. The anaphylactic antibody was qualitatively present in each of the precipitates.

4. Highly sensitized guinea pigs were appreciably protected from shocking doses of horse serum by specific water-soluble-antibody solutions.

5. Highly sensitized guinea pigs were completely protected against small multiples of shocking doses of horse serum by specific whole-globulin-antibody solutions and, by inference, by specific water-insoluble-antibody fractions.

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A COMPARISON OF PULMONARY AND DERMAL SENSITIVITY TO INHALED SUBSTANCES*

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DURING the last few years since cutaneous tests have been employed to determine clinical sensitivity to proteins, it has become apparent that they serve this purpose inadequately. If the results are not correlated with the clinical history and checked by the elimination of supposedly offensive substances, frequent errors in treatment occur. Rackemann[1] aptly considers that dermal tests form a composite picture of the past, present and future sensitivities of a patient. But this complex picture is still further confused by wide variations in the degrees of sensitization, and hence the thresholds at which various systems and the individual organs of each system respond to the same allergen. As a result of these divergences in sensitivity, dermal tests are often positive with minute amounts of an antigen which, in concentrations greater than those encountered in the normal life of the patient, fails to provoke a clinical response. The reverse of this situation is not uncommon. Pollens have been applied directly to the conjunctivae and to the nasal mucous membranes in instances where both dermal tests and the history failed to indicate the cause of hay fever. In a few instances allergens have been sprayed into the nose and throat during inhalation of the breath to demonstrate the etiologic relationship of uncommon allergens to asthma. Ordinarily in the study of a patient with asthma after cutaneous tests have been completed, elimination diets are used to determine the clinical sensitivities to foods to which the patient has shown dermal reactions, and a similar process of elimination is undertaken with substances which give off emanations which might be inhaled. For a time inhalation tests with extracts of feathers, textiles, and animal hair were carried out routinely in the clinic. The elimination of offending allergens from the patient's environments was thus greatly facilitated. Because this procedure was too time consuming and also because attacks of asthma lasting several days were occasionally provoked, routine testing by inhalation was discontinued. This experience, however, was exceedingly helpful in the future interpretation of dermal tests. By comparing dermal tests with the occurrence of asthmatic symptoms after inhalation of similar allergens, figures were obtained showing the relative value of the dermal test as an indication of clinical sensitivity of the bronchiolar mucous membrane.

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Forty-five patients with asthma between the ages of ten and fifty-five years were studied. These patients were first tested intradermally with ninety allergens including the common foods, epidermals, fabrics, and miscellaneous substances ordinarily causing asthma by inhalation. None of the patients had hay fever or pollen asthma. Tests to pollens were not included. The allergens for intradermal use were slightly alkaline solutions of specific precipitated proteins containing 1 mg. of nitrogen in 100 c.c. of solution. About 0.04 c.c. of these solutions were injected intradermally for each test. The results of the testing were recorded according to the size of the wheal and the area of erythema. Reactions with areas of erythema 6 cm. or more in diameter and wheals 2 cm. or more in size have been classed as "strongly positive." "Weak" reactions are those consisting of persistent erythema more than 2 cm. in diameter. All reactions with wheal formation between the "weak" and "strongly positive" have been considered "moderately positive" reactions. Many of the so-called "weak reactions" were possibly purely irritative and might not have occurred with scratch testing. Solutions of the extracts used in dermal testing but containing 20 to 25 mg. of nitrogen, were employed for the inhalation tests. The patient was taught to pinch the nose with the fingers and then to inhale deeply through the mouth. With each inhalation a fine spray forced from a small glass atomizer into the opened mouth was carried into the lungs. In highly sensitive patients two or three inhalations of the vapor were sufficient to cause asthma within two or three minutes. Some of the reactions were almost immediate. If asthma had not occurred within ten minutes after this preliminary inhalation of the allergen, larger quantities were inhaled until the operator was satisfied that clinical sensitization did not exist. Inhalation of spray or if necessary the administration of adrenalin subcutaneously was always sufficient to give immediate relief, although in many of the highly sensitive patients the asthma returned and lasted several days.

The cutaneous sensitivities were compared with the pulmonary reactions to seventeen allergens. Although the bronchial membranes were found sensitive on inhalation to extracts of some foods which caused asthma on ingestion, sensitizations to emanations only have been compared in the present study. The allergens included are duck, chicken and goose feathers; cotton, silk, sheep wool, flax, kapok and Florida moss; cat, dog, cattle, rabbit, and horse hair; orris, pyrethrum, and tobacco.

The patients fell naturally into two groups, according to the skin tests; one group with sensitive and the other with non-sensitive skins. Eleven of the forty-five were not cutaneously sensitive to any one of ninety common allergens. All of the inhalation tests in this group were negative. Each of the remaining thirty-four patients was der-

mally sensitive to some of the ninety substances used for routine testing. Among these patients fifteen had asthma after inhaling one or more of the extracts of feathers, hair or fabrics. In all there were twenty-five positive inhalation tests. Seven were to cotton, four to cat hair, three to kapok, three to chicken feather, and two to sheep wool. Single instances of sensitization were found to duck feather, rabbit hair, dog hair, silk, orris and Florida moss. Nine of the fifteen patients responded to only one allergen on inhalation, while three responded to two, two to three, and one to four of the inhalations. Some of the patients had additional food sensitizations. In this group of thirty-four dermally sensitive asthmatic individuals 578 dermal tests were done with the seventeen extracts previously enumerated. A corresponding inhalation test was done for each dermal test. Thirty-nine of the dermal tests were strongly positive, fifty-three moderately positive, seventy-six were weak, and 410 negative. Symptoms of asthma occurred seven times where the corresponding dermal test was strongly positive, six times with a moderate test, twice with a weak test, and ten times where the skin failed to react. The approximate ratios of pulmonary sensitivity to skin reactivity as derived from these figures were one to five when the dermis reacted strongly, one to nine with a moderate reaction, one in thirty-eight when the reaction was weak, and once in forty-one when the corresponding dermal reaction was negative. These figures apply, of course, only to those patients who are in the reactive group and are dermally sensitive to some of the common allergens. Subsequent studies have shown also, that these relative values are applicable only under the conditions in which the study was made; that they show the relationship of pulmonary sensitization to dermal sensitivity in asthma uncomplicated with allergic rhinitis or conjunctivitis.

CONCLUSIONS

With rare exceptions the pulmonary epithelium of asthmatic persons is clinically insensitive to feathers, epidermals, fibers of textiles, and miscellaneous material commonly found in the environments of the patients, if these patients belong to the so-called "non-reactive" or dermally insensitive group. If the skin reacts to any of these allergens or to the common foods, the bronchi and bronchioles are frequently sensitive to some material in the environment. Approximately half the clinical sensitizations to these materials are indicated by positive or strongly positive dermal tests. In about half the instances where the lungs are sensitive to these substances, corresponding dermal tests are negative or only faintly positive.

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MONILIA AND TRICHOPHYTON EXTRACTS; THEIR COMBINED USE IN ECZEMATOUS RINGWORM (DERMATOPHYTOSIS AND DERMATOPHYTIDS)*

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THE investigations of Van Dyck, Kingsbury, Throne and Myers[1] and of Sulzberger and Wise[2] have proved that repeated intradermal injections of extracts of fungi of the trichophyton group regularly desensitize the skin of patients originally hypersensitive to these extracts.

The patients treated were suffering from dermatophytosis and dermatophytid, an eczematous skin disease presumably due to the presence of fungi of the trichophyton group and/or their products; and to their dissemination to hypersensitive skin areas.

A certain number of cases were markedly benefited by this desensitization therapy. (Throne et al. had, on the whole, a far greater percentage of successful results with this method than Sulzberger and Wise.)

In the course of the reported and subsequent observations, Sulzberger and Wise noted that while trichophytin desensitization helped some cases of persistent and refractory dermatophytids in a manner which must be characterized as spectacular, other clinically apparently identical cases persisted in full strength despite trichophytin desensitization.

As the existence of trichophytin skin hypersensitivity has long been considered an obligatory accompaniment to a trichophytid or epidermophytid (Bloch[3]), this paradoxical persistence of epidermophytid-like eruptions in patients without trichophytin hypersensitivity required further study.

We can, at this point, only very briefly enumerate a few of the many possible explanations of this paradox. Among the most plausible to us are: (1) variations in hypersensitivity in different skin areas; for instance the skin of the arms or back, where the intradermal injections were performed, could beeome desensitized, while the skin of the hands or other sites of actual lesions retained a sufficiently high degree of trichophytin hypersensitivity to permit the continuation of the dermatophytid (for localized variations in eczematous hypersensitivity see

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J. Jadassohn,[4] Stauffer[5] and Sulzberger and Kerr[6]);* (2) a faulty diagnosis—many skin conditions clinically resemble dermatophytids and, in view of the almost universal prevalence in the United States both of fungus foci on the feet and of skin hypersensitivity to trichophytin, some cases due to other causes cannot be distinguished from dermatophytids by any known method.[2] Among the hand eruptions sometimes difficult to distinguish from "ids" are, first and foremost, eczematous dermatitis from contact substances, then vesicular and pustular drug eruptions, seborrheic dermatitis of the hands [exudative form], atypical psoriasis, etc.; (3) the eczematous hand and foot eruptions were "ids" (that is, secondary eruptions due to the reaction of a sensitized skin to disseminated microorganisms and/or their products emanating from a distant focus), but were not caused by fungi of the trichophyton group; they would thus not be specifically influenced by trichophytin desensitization.

In the study of the third possibility, common ubiquitous microorganisms, facultative pathogens such as staphylococci, streptococci (Jordan[11]) and monilia fungi had to be most seriously considered as etiologic factors.

Our reasons for selecting monilia fungi as the most likely cause of a certain percentage of trichophytin refractory "ids" may be summarized as follows:

(a) These fungi are found on all skins (Greenbaum and Klauder,[12] Bloch[13]), on the hair and nails (Jessner and Kleiner,[14] Becker and Ritchie[15]) and in the mouth and gastrointestinal tract (Hopkins[21]).

(b) They are capable of strongly sensitizing the skin (Ravaut and collaborators,[16] Staehelin et al.[17] and Biberstein and Epstein[18]).

(c) They can cause eczematous eruptions and elicit positive patch tests (Ravaut, Ramel and Benziger,[19] Sulzberger,[20] Sulzberger and Wise[2] [footnote 18], J. G. Hopkins,[21] Cleveland J. White, cited by Becker and Ritchie,[15] B. Shelmire, ibid. etc.).

(d) In spite of these many analogies with fungi of the trichophyton group, there is well-nigh conclusive evidence that the monilias form an immunologic group separate from the one embracing the trichophytons, epidermophytons, microsporons and achorions (Sulzberger and Kerr,[22] Sulzberger[23]).

The foregoing makes it obvious that some of the eczematous hand and foot cases could be caused by monilia (moniliids); and that, in these, trichophytin desensitizations would not have a specific therapeutic effect. This would account for some of the trichophytin refractory cases. (Trichophytin is used as the generic name for ex-

*We are purposely avoiding the discussion of the complex question of positive anergy, which might, of course, account for some dermatophytids with negative trichophytin reactions. (See Matras[7], Pels and Schlenger[8] and, for tuberculin anergy, J. Jadassohn,[9] Sulzberger and Wise.[10])

tracts from only those fungi which are included in the trichophyton, epidermophyton, microsporon and achorion groups.)

It seems to us that the only logical conclusion to be drawn from all of these facts is that (after elimination as far as possible of the likelihood of contact dermatitis and dermatitis from other causes) persistent and severe eruptions of the hands and feet with the clinical appearance of dermatophytids should be skin tested and desensitized not only with trichophytin but with oidiomycin (monilia extract) as well.

Approximately a year and a half ago, we began to enlarge the scope of our investigations to include desensitization with monilia as well as with trichophyton extracts.

In these investigations we employed fungus extracts kindly prepared for us by Dr. A. F. Coca of Lederle Laboratories. These extracts were made with Br. Bloch's modification of the original technic of Plato-Neisser in the preparation of trichophytin. One of us has described this method in detail elsewhere.[23]

The fungi employed were: for the *oidiomycin*, a pathogenic strain of *monilia albicans* from a typical severe skin moniliasis; and, for the *trichophytin*, a strain of *epidermophyton interdigitale* (trichophyton interdigitale epidermophyton of Kaufmann-Wolff) from a severe eczematous mycosis of the feet.

Before proceeding to actual attempts at desensitization, we standardized these extracts in quantitative and comparative studies. We employed dilutions of from 1:1,000,000 to 1:10 of the extracts in normal saline. The investigations were carried out on a series of 25 cases in the Dermatological Clinic of the Post Graduate Medical School and Hospital of Columbia University. Four of the twenty-five patients had skin eruptions generally attributed to primary monilia infection *(erosio interdigitale*, water bath mycosis of Kraepelin, *intertrigo oidiomycetica)*. The remaining twenty-one suffered from miscellaneous skin diseases, including the clinical picture of dermatophytosis and dermatophytid.

With full consciousness of the danger of drawing conclusions from such a small number of cases, we nevertheless wish to report our results, as we believe that these investigations are the first to be carried out with exact quantitative intradermal tests and comparisons between monilia and trichophyton extracts.

Our conclusions (not to be generalized, but to be regarded as applicable to our cases only and only to the extracts we employed) may be summarized as follows:

(1) Extracts of monilia albicans (hereinafter called "oidiomycin") elicited a positive intradermal reaction of the late papular, i.e., tuberculin and trichophytin type (acme usually twenty-four to forty-eight or more hours after injection) in the majority of patients.

(2) Fungi of the monilia group are strong sensitizers. We came to consider it normal for a patient to have a slight to moderate reaction to 0.1 cc. of oidiomycin in a dilution of from 1:500 to 1:100. (This corresponds to the normergic or average trichophytin reaction which, in adults in American cities, seems to be slight to moderate—0.1 c.c. of trichophytin in dilutions of from 1:30 to 1:50. [Rosin, Peck, and Sobel[24] White and Taub,[25] Pels and Schlenger[8] and References 1, 2, and footnote in Ref. 22.])

(3) Trichophytin hypersensitivity and oidiomycin hypersensitivity are separate and distinct one from the other, both in the late papular tuberculin type of reaction and in the eczematous reaction to patch test. This confirms the sharp immunologic separation of these two fungus groups, which has been demonstrated previously through other forms of immunologic investigation.[22, 23]

(4) A positive oidiomycin reaction may, in all probability, be considered, in analogy to tuberculin and trichophytin and other reactions of this type, as evidence that contact with and sensitization to monilia have taken place. This view is also supported by various other authors and by the experiments of Biberstein and Epstein, etc.[18]

Tests on infants before possible contact with monilia, and on groups of children of various ages, will clarify this point. For the present, the oidiomycin reaction must be classified as *specific*.

However, just as in the case of trichophytin, the reaction is not in its present state *diagnostic*. (Ref. 2, and footnote in Ref. 22.) For we have observed, just as Biberstein and Epstein and others have already reported,[17, 18] individuals without manifest oidiomycotic disease and without history of such disease, who had, nevertheless, extremely strong reactions to oidiomycin.

It still seems possible that quantitative studies on a very large clinical material, combined with the most careful mycologic studies, may eventually develop a monilia test of a modified or relative diagnostic value. This has been the development in the case of the tuberculin test. (For an English summary of the use of tuberculin in dermatology, see J. Jadassohn,[9] and Sulzberger and Wise.[10])

(5) With our extracts and in our cases, we observed neither the 100 per cent immediate wheal reaction to oidiomycin, reported by Staehelin et al.,[17] nor the late reaction of Ravaut in levurides.

(6) Among 12* cases of eczematous hand and foot eruptions clinically called dermatophytosis and dermatophytid (in the large majority of which it may be assumed that both the omnipresent monilia and the almost omnipresent epidermophyton could have been found by careful mycologic investigation of the feet, toenails, mouth, etc.) there were *none* with skin reactions to trichophytin alone, 8 cases with reac-

*Six cases observed at the Post Graduate Clinic and six cases at the office of Wise and Sulzberger, reported in detail below.

tions to both trichophytin and oidiomycin, and 4 cases with reactions to oidiomycin alone.

These results and the theoretical considerations stated prompted us to the trial employment of oidiomycin desensitization as additional immunologic therapy in persistent cases of clinical dermatophytosis and dermatophytid.

The results of these attempts are, in general, not yet ripe for final decision. However, this much may now be said: Repeated intradermal injections of monilia extract bring about a desensitization of the skin to these extracts. Patients previously reacting violently to 0.1 c.c. of a 1:500 or 1:1,000 concentration of oidiomycin could generally, by careful and persistent treatment, be brought to tolerate 0.1 c.c. of a 1:10 concentration of the same extract. *This fact must be stressed.* It is, as far as we can ascertain, *the second specific, systematic and therapeutic desensitization of the skin to the products of microorganisms, as far as intradermal injections and reactions of the tuberculin type are concerned.* The previous one recorded is the desensitization to trichophytin.[2] This addition of a second example of successful intradermal desensitization makes it probable that we are dealing with an immunologic principle which may have a certain general significance.* It suggests the possibility of expanding the therapeutic method of controlled, systematic, quantitative intradermal desensitization to include general diseases (tuberculosis, etc.) and of embracing within its scope desensitizations to other organisms (staphylococci, streptococci, etc.) in the treatment of both sensitization dermatoses and of other diseases of bacterial sensitization.

While we are, as yet, unable to state how many cases of so-called dermatophytosis and dermatophytid are due to sensitization by oidium rather than by trichophyton, or how many may be due to still other microorganisms (staphylococci, etc.), we have the distinct impression that some of our cases were very definitely benefited by including monilia desensitization in the immunologic therapy. We should like to cite a few examples from the practice of Wise and Sulzberger, illustrating not only the therapeutic effects of oidiomycin and combined desensitization, but also some of the difficulties encountered and the many sometimes inexplicable immunologic phenomena observed in the course of these desensitizations.

CASE REPORTS

CASE 1.—J. L., a girl aged ten years, had a severe vesicular eruption of the hands and feet, appearing intermittently during a period of four years. The dermatitis cleared under topical treatment and x-ray

*Some records of intradermal desensitizations have been made in other bacterial and nonbacterial conditions, but as far as we have been able to find, no systematic therapy on large groups has been reported. (For tuberculin, see Bessau, cited by R. Volk,[27] W. Jadassohn.[26]

therapy, only to recur repeatedly. Skin tests, intradermal and patch, showed that trichophytin extract in a concentration of 1:30 caused no reaction; while with oidiomycin 1:100 the reaction to intradermal test (tuberculin type, forty-eight hours) was four-plus, and to 1:1,000 was one-plus. The patch test with oidiomycin was also positive.

Intradermal injections of the monilia extract were given twice weekly, and the child became rapidly desensitized to increasing concentrations up to oidiomycin 1:10. After ten injections, the skin lesions disappeared entirely. Six months later there was a recurrence of a vesicular eruption on hands and feet. Testing at this time showed oidiomycin extract intradermal 1:100 negative, and 1:10 mildly positive. Therapeutic injections were renewed, and after four or five injections the reaction became much stronger. At present, after 17 injections, the reaction is again only slight at 1:10 and the skin lesions are much improved but not entirely gone.

CASE 2.—T. Z., a young woman aged nineteen years, presented in March, 1932, severe vesicular lesions of one foot and both hands, with maceration and scaling between the toes. There was little change in the condition under local treatment. Four months later, the patient had an acute generalized vesicular eruption of erythema multiforme exudativum type. This subsided gradually under local medication, and the original eruption of the hands and feet also disappeared. Ten months later, there was a severe recurrence of a similar dermatosis on hands, arms and between the toes. One lesion on the arm was a ring the size of a twenty-five-cent piece with complete clearing in the center and peripheral pinhead-sized vesicles. At this time, testing with trichophytin 1:100, both intradermal and patch, caused no reaction.* Oidiomycin 1:100 intradermally elicited a three-plus positive reaction; the patch test with oidiomycin was negative. Desensitization was started with oidiomycin 1:100, and after four injections the reaction became much less severe, so that 1:50 could be given, and finally 1:10. After eleven injections, the original skin eruption was almost gone.

CASE 3.—R. T., a man aged twenty-seven years, had a papulovesicular dermatosis on the arms, hands and upper back for three years. There were no foot lesions present, nor any history of scaling or maceration between the toes. Many of the lesions began as pinhead-sized papule. This was very pruritic, and soon several similar agminated papules appeared until finally a coin-shaped lesion was apparent. The discoid dermatitis thus formed became exudative and crusting. Healing proceeded with definite clearing in the center, and annular lesions were thus produced. An accompanying sharply demarcated scaling of the scalp was present, and at first the diagnoses of papulovesicular seborrheic dermatitis or of contact dermatitis were considered. Under local

*For experiments with and discussion of the patch test in eczematous mycotic eruptions, see Sulzberger and Lewis.[28]

treatment, the lesions disappeared, only to return six months later in a more severe form. At this time, tests with trichophytin 1:30 intradermally and with a patch test were negative at both twenty-four-hour and forty-eight-hour readings. A week after application of the extract, both test areas reacted with a response which was recorded as two-plus. Oidiomycin 1:10 intradermally was four-plus on twenty-four-hour reading. The arm was swollen and the axillary lymph glands were enlarged. The oidiomycin patch test was, at first, negative, but a week later a few vesicles appeared.

Desensitization was begun with high dilutions of both trichophyton and monilia extracts, respectively 1:100 and 1:500. After the seventh injection, a pruritic follicular dermatitis broke out on the face. This subsided in ten days. Delayed reactions to trichophytin injections continued to occur. The reaction at the intradermal trichophytin site regularly took from five to seven days to reach its acme, while the oidiomycin site showed its maximum reaction in approximately forty-eight hours.

During the beginning of the course of treatments, headaches appeared regularly two days following each injection.

To date, fourteen injections have been given at weekly intervals. The reactions, though diminished in severity, are still occurring. There are focal flare-ups three to four days after injections. The skin lesions seem to have responded to this treatment, for they are greatly decreased in size and number, and the subjective symptom of a distressing itch has almost completely subsided.

Case 4.—Mrs. W. H., aged forty-five years, had been suffering for twenty-six years from a persistently recurring vesiculopustular eruption of the right hand. There was slight scaling between several toes, and there were many empty vesicles (keratolysis exfoliativa) on hands and feet. Testing with trichophytin 1:30 intradermally showed a four-plus reaction, while the patch test was negative; oidiomycin 1:100 intradermally gave a three-plus reaction and a negative patch test. For three days and nights after these injections, there were spells of sneezing, running of the nose and swelling of the mucous membranes of the nose and throat, accompanied by a general feeling of malaise. Because of these symptoms, very low desensitization doses of trichophytin and oidiomycin were given. The vasomotor rhinitis-like by-effects decreased in severity coincidentally with the progressively decreased skin reaction at the sites of the successive intradermal injections. As the strength of the fungus filtrate was increased, the sneezing and swelling of the mucous membranes became more severe, but decreased in the course of the next few injections, until the concentration of the vaccine was again stepped up. At every injection, there was a focal flare-up of the skin lesions on hands and feet.

The patient has had twenty injections, the tolerance for fungus extracts has greatly increased, and the dermatitis has almost disappeared.

CASE 5.—Mrs. H. M., aged fifty-three years, presented a severe vesiculosquamous disseminated eruption of the arms, hands and legs, of one and one-half years' duration. There were deformity and opacity of all the toenails (onychomycosis ?). The results of tests were as follows: trichophytin 1:30 intradermally elicited a two-plus reaction; the patch test was negative. Oidiomycin 1:500 intradermally caused a four-plus reaction, with accompanying edema of the entire upper arm. The patch test was negative.

We commenced therapeutic intradermal injections with both trichophytin and oidiomycin. These brought about results which at first seemed astonishing and paradoxical, but which we have learned to recognize as usual phenomena. The originally rather weak trichophytin reactions increased in severity with successive trichophytin injections; and the originally very marked oidiomycin reactions became rapidly less with every injection of the monilia extract. There was a remarkable decrease in the strength of the oidiomycin reaction and a very definite improvement in the skin lesions after only one injection. Desensitization with both vaccines was continued, and the patient when last seen was almost cured.

CASE 6.—Patient H. B., a man aged thirty-one years, had a vesiculopapular dermatitis on hands and arms, with scaling and maceration between the toes, recurring during three years in spite of topical and x-ray treatment. Skin testing showed: trichophytin 1:30, intradermally and patch, strongly positive; oidiomycin 1:500 intradermally, four-plus, and patch test negative. Desensitization with trichophytin was rapid—only eight injections being required to desensitize to the point of absence of reaction at the strength of 1:30. During this time, the local lesions were only slightly improved. However, after two oidiomycin injections (1:100), the lesions became definitely better. At the time of this marked clinical improvement, the response to concentrated trichophytin was still four-plus. A generalized pruritus occurred after each injection. The eczematous dermatitis disappeared, and the patient was discharged after five injections of combined trichophytin and oidiomycin.

Eight months later, a new eruption appeared on the hands. Testing showed the patient to be trichophytin 1:30 negative, but oidiomycin 1:100 three-plus. Five injections of oidiomycin caused desensitization and clinical improvement. We then retested the patient with trichophytin and found him to react strongly to the undiluted extract. Injections of trichophytin (undiluted) alone were given, but the lesions on the hands became worse. Upon again starting oidiomycin 1:100, a reaction was elicited and the eruption on the hands and

arms began to improve immediately. After eight injections, the patient was desensitized to oidiomycin 1:50, his skin was normal and he could be discharged from treatment.

Even an approximately adequate discussion of our knowledge (and, more particularly, the gaps in our knowledge) concerning the dermatoses caused by fungi of the monilia and trichophyton groups would obviously require far more space than permitted in this paper. There are here still many points under discussion. For instance, in spite of the assiduous research of recent years, while the fundamental processes are known, there is no unanimity of opinion regarding certain points in the pathogenesis of dermatophytids in general. It is also obvious that the differentiation, classification and possible pathogenicity of the various monilias, oidia, cryptococci, blastomyces, etc., require much further study (Hopkins,[21] Staehelin et al.,[17] Biberstein and Epstein,[18] Bloch[3]).

Although our results have bearing on some of these points, we shall be forced to commit numerous sins of omission. We shall have to limit ourselves to the following summary and brief discussion of some of our findings, viewed and evaluated in conjunction with previously established theories and facts.

SUMMARY AND DISCUSSION

1. Fungi of the monilia group are practically ubiquitous, being present in intertriginous and other areas of nearly all skins, as well as in the toenails, mouths, gastrointestinal tracts, etc., of most persons.

2. Fungi of this group are strong sensitizers and capable of producing both primary skin infections and secondary eczematous eruptions (moniliasis and moniliids). In this, they closely resemble the trichophyton interdigitale group in their action.

3. The sensitizations caused by fungi of the monilia group and by fungi of the trichophyton group are apparently specific to each group and not immunologically identical. Previous observations on this point are substantiated and enlarged by our present findings. For, in our group of twelve clinically typical cases of dermatophytosis and dermatophytid, while eight were hypersensitive to intradermal injections of both trichophytin and oidiomycin, four (or one-third of the total number) were *not hypersensitive to trichophytin, but to oidiomycin alone.* Furthermore, one patient hypersensitive to both trichophytin and oidiomycin had consistently different reaction times to the two extracts; the oidiomycin reaction always reached its acme about forty-eight hours after injection, while the trichophytin reaction was at its height after an interval of from five to seven days (Case 3).

These findings also prove that the skin reactions are due to specific substances of the fungi themselves, and not to the culture broth or other fortuitous accompanying substances. (In previous experiments

carried out with only one fungus extract [trichophytin], we have always found it necessary to employ control skin tests with uninoculated culture broth to be certain that the fungi were the causes of the reactions elicited.)

Not only was the tuberculin (late papular) type of reaction specific for each of the two fungus groups, but patch test reactions (eczematous epidermal response) showed an identical specificity (certain patients were positive to patch tests with both oidiomycin and trichophytin, while others were positive to one or the other alone).

4. In our group (30 cases), the average adult reacted with a slight to moderate response (acme twenty-four to forty-eight hours after injection) to intradermal skin test with 0.1 c.c. of a 1:100 to 1:500 dilution of the monilia albicans oidiomycin which we employed. This corresponds to the average adult reaction to 0.1 c.c. of a 1:30 to 1:50 concentration of the various trichophytins which we used.

5. It is, in our opinion, a probability approaching certainty that the positive reaction to intradermal oidiomycin is evidence of a sensitization due to previous intimate contact with monilia or immunologically related fungi; and *is, therefore, specific.* However, just as with trichophytin, the reaction is *not diagnostic,* i.e., we have not been able to find a means of testing nor a concentration of extract through whose employment one could *prove the presence of actual active monilia disease.* Most persons (probably because most have had intimate contact with monilia, at some previous time) have a skin hypersensitivity to oidiomycin. We have not infrequently observed persons with a very high degree of hypersensitivity to oidiomycin, who had no evidence of past or present disease due to monilia.

6. Desensitization to oidiomycin can be achieved by the same method and technic as that successfully employed with trichophytin (repeated systematic intradermal injections of very gradually ascending doses). We did not note any definite cross-immunization between trichophytin and oidiomycin. Patients originally hypersensitive to both extracts when desensitized to one remained hypersensitive to the other. This again shows the immunologic separation of these two fungus groups.

7. While some cases of persistent typical clinical dermatophytosis and dermatophytid are arrested when their skins are desensitized to trichophytin, others, in apparently paradoxical fashion, persist in full severity even when desensitized to products of trichophyton fungi. In such cases, other ubiquitous, sensitizing microorganisms must be considered as possible etiologic agents. In consideration of all the facts summarized, fungi of the monilia group must, in our opinion, bear the brunt of suspicion. We believe with Br. Bloch[29] that streptococci and staphylococci, as well as other microorganisms and substances may play a rôle in the causation of certain cases of "ids"; but this point must be the object of further study. Bloch has coined the

term "microbids" for these secondary allergic manifestations caused by sensitizing microorganisms in the skin and internal organs. It is our impression that this conception is of the most fundamental importance for the future study of the pathogenesis of all infectious diseases.

8. In desensitization experiments with oidiomycin, we observed those phenomena which are frequently encountered in this type of immunologic process in general and which have been previously noted in connection with trichophytin: namely, focal flare-ups of the lesions, annular forms at the injection sites, regional lymphangitis and lymphadenitis after intradermal injection, general feeling of malaise, headache, and increased pruritus after injection. Furthermore, one case (Case 4) had typical vasomotor rhinitis after each and every injection (Wise and Sulzberger[30]). One case (Case 2) had an erythema multiforme-like eruption which was possibly a form of oidiomycid (see Br. Bloch[31] for summary of cases of erythema multiforme as a trichophytid).

9. Moreover, just as in other active immunization procedures (trichophytin, tuberculin), we observed that in oidiomycin desensitization the active immune or desensitized stage may sometimes be reached by passing through a stage of increased hypersensitivity. A weak response to oidiomycin may increase in strength with successive injections. Apparently, only after the hypersensitivity has reached its acme, does the desensitization begin. This increase in hypersensitivity is one of the difficulties encountered in the therapeutic use of desensitizations; and it requires skill, patience and judgment to pilot the patient through the hypersensitive phase. In choosing patients for this treatment this must be borne in mind.

10. Satisfactory therapeutic results, through desensitization either with oidiomycin alone or with oidiomycin plus trichophytin are reported in six persistent cases of clinical dermatophytosis and dermatophytid.

The theoretical considerations outlined, supported by our observations and therapeutic results seem to us to warrant the conclusion that *combined oidiomycin-trichophytin desensitization is the logical therapeutic procedure in persistent cases of eczematous hand and foot eruptions due to fungi. Since it is today almost impossible to say which of these two groups of practically omnipresent and sensitizing fungi may be the main pathogenic agent in a given case, routine combined desensitization with both groups seems the most rational measure.*

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SOY BEAN AS A POSSIBLE IMPORTANT SOURCE OF ALLERGY*

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SOY bean, soy bean flour, soy bean meal and soy bean oil are known as such to very few lay people and to very few doctors except in relation to diabetic foods and certain prepared foods. The fact is, however, that soy bean is used for so many different purposes, 250 or more, that its distribution is almost universal. It is commonly mixed with flour and is found therefore in many breads. It is used in breakfast foods, diabetic foods, cakes, muffins, biscuits, infant foods, crackers, and macaroni. It is used also in the make-up of soups, coffee substitutes, and in fresh milk, condensed milk, and in confections and sauces. It is also used as a fresh vegetable and as canned beans and in salads. It is used for fodder and fertilizer. Soy bean oil is used as a substitute for butter, lard, and salad oil. It is used in making linoleum, paints, soap, celluloid, rubber substitutes, printing ink and for lubricating.

A patient, aged forty-three years, employed in a soy bean mill, came to me with the story that he could not escape from soy bean regardless of where he lived. The fact is that his residence was on one side of a soy bean mill and his office on the other, and depending upon wind direction he would have asthma at his home or in his office.

He stated positively he could not escape soy bean in his diet and was so sensitive that he would have asthma if he drank milk obtained from cows fed on soy bean fodder.

He brought with him various and sundry products derived from soy bean. All of them, including soy bean oil, gave enormous positive skin tests. Scratch test edema was no less than one inch in width and erythema covered an area twice as wide. He gave strongly positive tests to all members of the legume group, to Bermuda and crab grasses, and to giant and short ragweed. Other tests were negative.

The oil was interesting in that if it was filtered through stone it ceased to cause reaction. Consequently we can assume that soy bean oil is inert and that the agent responsible for reaction to commercial soy bean oil was not the oil but invisible particles of soy bean contained in the oil.

Passive transfer was obtained with unusual ease, and passively sensitized areas of the skin of nonsensitive individuals reacted to every

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extract of the pea and bean group which was tried. Also peas and beans desensitized areas passively sensitized to soy bean.

An interesting feature of the excitant was the fact that it was almost indestructible. An extract of soy bean meal was autoclaved, boiled with dilute sodium hydroxide, boiled with dilute HCl, precipitated with heat and acetic acid, precipitated with picric acid and with Esbach's reagent and in spite of all this the respective filtrates passed through stone would give strongly positive scratch tests—in fact some of the treated filtrates were more positive than the original extracts, because, I believe, of the fact that removal of gross amounts of protein material from the original viscid extracts allowed a more rapid penetration into the tissues of the watery-like treated extracts.

I cannot express a definite opinion concerning the excitant at the present time except to say that any protein excitant which can stand autoclaving for one-half hour and boiling for two hours with dilute hydrochloric acid and dilute sodium hydroxide without being rendered completely inert is a pretty tough material. Dr. Coca was kind enough to study the serum and soy bean extract and stated that the excitant can be proved to be a protein by desensitization of passively sensitized areas.

Four additional individuals who worked in the soy bean mill and who had cough and asthma were tested with soy bean extract. Two gave scratch reactions ¼ inch wide, one a scratch reaction ¾ inch wide, and one a reaction almost 2 inches wide. The ratio of positive tests is grossly greater than that found in allergy patients seen in my office. The latter give positive tests in about the same proportion of cases as the other members of the legume group and seem to have a group similarity with the legumes.

This case is analogous to Figley's study of patients sensitive to castor bean dust. The patient was treated with soy bean extract in small ascending doses with great relief. However, we have not yet succeeded in raising the dose to a point which gives complete relief upon gross exposure to soy bean dust.

SUMMARY

Soy bean has a wide or almost universal distribution. Both the oil and the flour are used in many sorts of foods mentioned in the text and as a fertilizer and for fodder.

Five patients working in a soy bean mill who were subject to cough and asthma gave positive reactions to soy bean extract.

Sensitiveness was passively transferable and sensitized areas could be desensitized by other members of the legume group in one case which could be adequately studied.

The patient whom I treated with ascending small doses of soy bean extract was definitely benefited so that with the use of a mask and avoidance of dust around the mill he keeps himself free of asthma.

It is believed, because of the number of cases of soy bean sensitiveness found in the mill, that soy bean is probably an important cause of asthma in the region of soy bean mills. It probably is a cause but a less common cause of asthma in other regions.

The possibility of this sensitization should be looked for especially in individuals whose occupation or habits bring them in frequent contact with soy bean products.

ACTIVE TRANSMISSION OF URTICARIA BY BLOOD TRANSFUSION

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IN AN excellent review of reactions to blood transfusions, Polayes and Lederer[1] state that allergic reactions to blood transfusion are not uncommon. Duke[2] in a review of 700 transfusions says that a history of allergic phenomena in an individual is an important contraindication to his use as a donor. A search of the literature does not reveal any reports of the active transmission of urticaria by blood transfusion.

The following case report thus seems to be of considerable interest.

A male, aged twenty-eight years, whose occupation was given as a laborer, was fatally ill with acute aplastic anemia, apparently secondary to chronic benzol poisoning. A series of thirteen whole blood transfusions was given him over a period of four weeks. Repeated frequent transfusions were necessary because of continuous bleeding from gum margins, kidneys, and gastrointestinal tract. The patient belonged to group three, and all donors used belonged to the same group. In addition, each donor was cross-matched with the recipient and a perfect match resulted in each instance. For the seventh transfusion, a brother-in-law of the patient was selected. About thirty minutes following the transfusion, consisting of 500 c.c. of whole blood given by the direct method, the recipient developed a generalized urticaria accompanied by very intense pruritus. The urticaria and itching were both relieved by adrenalin hypodermically. Subsequent questioning of the donor revealed that he had had generalized hives at the time of the transfusion. He was sensitive to strawberries, and the urticaria had developed following ingestion of these berries. The recipient had no history of previous allergic phenomena, and later he was given strawberries without developing urticaria. About two weeks later this patient received his twelfth transfusion, and his brother-in-law was again used as the donor. The donor did not exhibit urticarial phenomena at the time, and no hives developed in the recipient following this transfusion which was conducted under the identical conditions of the previous transfusion.

Passive transmission of human hypersensitiveness by blood transfusion was first observed by Ramirez.[3] The donor was an asthmatic individual sensitive to horse dander. The recipient subsequently had asthmatic attacks when he came in contact with horse dander. Re-

cently Holder and Diefenboch[4] have also reported its occurrence following a whole blood transfusion. Their patient was ill with agranulocytopenia and received two transfusions along with other therapy. Following her discharge from the hospital she had several attacks of urticaria, which she had never previously experienced, following ingestion of strawberries. Subsequent questioning of the second donor revealed that he had had violent urticarial reactions following eating of strawberries all his life.

Duke and Stofer[5] have reported allergic reactions developing in sensitive persons who were transfused with the blood of donors who had previously ingested substances to which the recipients were sensitive. To prevent such reactions Brem, Zeiler and Hammack[6] have emphasized the importance of using fasting donors.

Böttner[7] has reported several instances of allergic reactions developing after repeated transfusions of compatible blood. The reactions developed following those transfusions that were done three to six weeks after the first.

Smyth[8] has reported immediate wheal formation at the site of injection following intracutaneous injection of serum from certain infants with active eczema into the skin of normal infants. He considers the reaction to be due to the transfer of an irritating substance circulating in the blood of the eczema patient. This irritant resembles the "histamine-like" substance described by Lewis and Grant.[9]

In the case reported above, it seems likely that the specific substance responsible for the production of hives in the recipient was circulating in the donor's blood stream at the time of the transfusion and thus was transmitted to the recipient. After being acquired by him, a generalized urticarial reaction followed.

CONCLUSIONS

1. The case report of a patient who developed active urticaria following direct transfusion of whole blood from a donor who was suffering with urticaria is presented.

2. The urticaria was undoubtedly due to the transmission by the transfusion of the active substance in the blood responsible for producing urticaria originally in the donor.

3. This substance is probably the "histamine-like" substance of Lewis.

4. Greater care should be exercised in investigating the allergic history of all prospective donors.

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THE POLLEN CONTENT OF THE AIR IN TORONTO, CANADA, 1932*

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THE investigations reported in this paper were instituted a number of years ago, but only led up to a continuous and systematic survey of the atmospheric pollen in this city for a year beginning the latter part of March, 1932. The work includes not only a study of the pollen content of the air, but also daily field observations from the time the early trees began to bloom in the spring until the first killing frost in the fall.

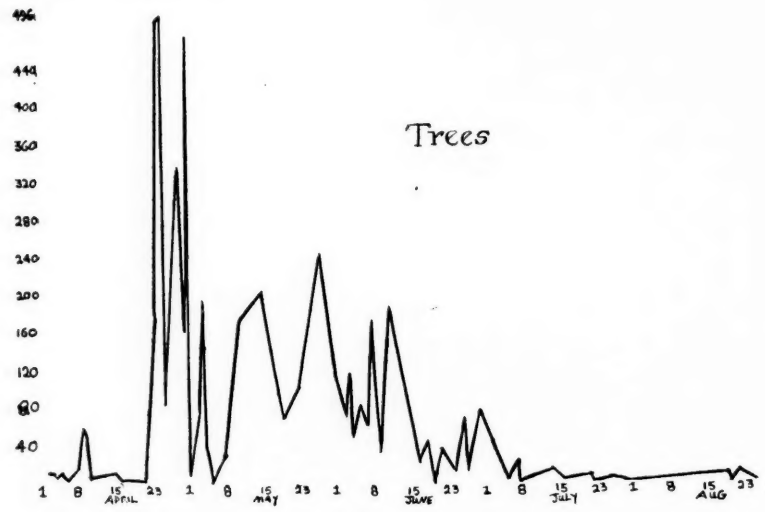

Fig. 1.

Since the charts and graphs are self-explanatory, the method will be only briefly outlined in order to give some idea of the manner in which the work was conducted.

Vaseline coated microscopic slides were exposed at seven stations located in different parts of the city, taking in an area of approximately forty square miles. A metal trap was so constructed as to hold five slides, four of which were placed in an upright position, one facing each direction of the wind, and one placed in a horizontal position. These were changed every twenty-four hours. The num-

*From the laboratory division of the Chest and Allergic Clinic of the Dept. of Pensions and National Health at Christie Street Hospital, Toronto, Canada.

TABLE I

1932	ACER SACCHARINUM	EQUISETUM—SPP	ACER RUBRUM	PINUS—SPP	ULMUS—SPP	ALNUS—SPP	POPULUS—SPP	BETULA—SPP	ACER NEGUNDO	FAGUS—SPP	PUSSY WILLOW	FRAXINUS—SPP	ACER PLATANOIDES	UNIDENTIFIED	SLIDES EXPOSED	TOTAL	AVERAGE PER SLIDE	WIND	WEATHER
April 1															21			S.W.	Cloudy
April 2	12														21	12	6	N.E.	Snowing
April 3	11														21	11	5	N.W.	Cloudy
April 4	6														1	6	6	N.E.	Clear
April 5	8														21	8	4	N.E.	Fair
April 6	21														21	21	1	N.W.	Cloudy
April 7	6														21	6	3	N.E.	Clear
April 8	16														21	16	8	N.W.	Cloudy
April 9	60														1	60	60	N.E.	Cloudy
April 10	49														1	49	49	N.E.	Cloudy
April 11	6														21	6	3	– E.	Cloudy
April 12		1													21	1	1	S.W.	Cloudy
April 13															1	1	1	N.W.	Fair
April 14															21	1	1	S.W.	Fair
April 15			10												21	10	5	– S.	Fair
April 16			6												21	6	3	N.W.	Fair
April 17			4												21	4	2	N.W.	Fair
April 18			1												21	1	1	N.W.	Fair
April 19			21	1											21	3	1	N.W.	Fair
April 20			1												21	1	1	S.E.	Fair
April 21			10		166	4								8	21	180	90	– E.	Fair
April 22			1		495	4									21	508	254	S.W.	Fair
April 23			21		490	21									21	494	247	N.W.	Fair
April 24			1		362	21									21	368	184	– S.	Fair
April 25			21		82										21	84	42	N.E.	Cloudy

TABLE I—CONT'D

1932	ACER SACCHARINUM	EQUISETUM—SPP	ACER RUBRUM	PINUS—SPP	ULMUS—SPP	ALNUS—SPP	POPULUS—SPP	BETULA—SPP	ACER NEGUNDO	FAGUS—SPP	PUSSY WILLOW	FRAXINUS—SPP	ACER PLATANOIDES	UNIDENTIFIED	SLIDES EXPOSED	TOTAL	AVERAGE PER SLIDE	WIND	WEATHER
April 26															2	–	–	N.W.	Cloudy
April 27			3		160									3	2	172	86	N.W.	Fair
April 28					253	2									2	255	127	N.W.	Fair
April 29			4		335										2	339	169	– E.	Fair
April 30					156	8									2	164	82	– E.	Rainy
May 1			4		476									1	2	481	240	S.W.	Cloudy
May 2					16									2	2	18	9	N.W.	Cloudy
May 3			6		67									1	2	74	37	– S.	Clear
May 4					160	3	32								2	195	97	S.W.	Cloudy
May 5					16	2	15								2	33	16	S.E.	Cloudy
May 6								1							2	1	–	N.E.	Cloudy
May 7					4				2						2	6	3	N.E.	Rain
May 8					13			3	12						2	28	14	N.E.	Cloudy
May 9					12			2	3						2	17	8	N.E.	Cloudy
May 10					9		10		4						2	23	11	N.E.	Cloudy
May 11							20	5	40						2	65	32	N.E.	Cloudy
May 12							2	142	8	3	18			1	2	174	87	N.E.	Fair
May 13					4			234	12	2	7	29		2	2	290	145	S.W.	Fair
May 14					2		1	147	8	4	8	51		1	2	222	111	S.E.	Fair
May 15					1		1	89	6	5	3	97		4	2	213	106	– E.	Fair
May 16								30		1		2		1	2	34	17	S.E.	Cloudy
May 17								21		2	5	105	3		2	136	68	– W.	Fair
May 18								52			6	186	12	1	2	257	128	– S.	Fair
May 19								22		6	18	20	4		2	70	35	S.E.	Fair
May 20								2			2	6			2	10	5	S.W.	Fair

TABLE II

1932	PINUS—SPP	POPULUS—SPP	BETULA—SPP	PUSSY WILLOW	FRAXINUS—SPP	ACER SACCHARUM	QUERCUS—SPP	PYRUS MALUS	MAGNOLIA—SPP	AESCULUS—SPP	TSUGA CANADENSIS	ACER PSEUDO-PLATANUS	SALIX—SPP	GINKGO BILOBA	POA ANNUA	BERBERIS JAPONICA	EUROPEAN MT. ASH	POA PRATENSIS	PHILADELPHUS CORONARIUS	UNIDENTIFIED	SLIDES EXPOSED	TOTAL	AVERAGE PER SLIDE	WIND	WEATHER
May 21				3	11																2	14	7	N.W.	Cloudy
May 22	2	1	28	9	90	12	4	1	1											1	2	149	74	S.E.	Clear
May 23	1	1	26	8	36	21	5	2												3	2	103	51	N.W.	Fair
May 24	1		21		20	18	20	1		1											2	82	41	S.W.	Clear
May 25	2		24	6	28	4	36													5	2	105	52	– W.	Cloudy
May 26	2		8	6	8		32	2	1											6	2	65	32	S.W.	Cloudy
May 27			37	3	39		115				9	7	3							8	2	221	110	S.W.	Cloudy
May 28	9		39				175	2		2	6	13	1							7	2	248	124	N.W.	Cloudy
May 29	12		10				60				18	3		1							2	104	52	N.W.	Fair
May 30	8						50	1			10	2		1							2	72	36	S.W.	Fair
May 31	6						30	1			21	1		1						9	2	69	34	N.W.	Clear
June 1							106				8										2	114	57	N.E.	Fair
June 2	4						49					5			1						2	59	29	N.E.	Cloudy
June 3	37						20				8	1			1					8	2	75	37	– E.	Cloudy
June 4	110										8				2					3	5	123	24	– S.	Clear
June 5	38										10				3					2	5	53	11	S.W.	Fair
June 6	60						14				6				5	1				3	5	89	18	N.W.	Clear
June 7	40						10				3				8	1	6			1	5	69	14	N.E.	Clear
June 8	160						3				2				4		3	4	2		5	178	36	N.W.	Fair
June 9	40										3				4		2	3		3	5	55	11	N.W.	Fair
June 10	15						5				4				5		1	3		3	5	36	7	N.E.	Fair

TABLE III

1932	EQUISETUM—SPP	PINUS—SPP	QUERCUS—SPP	TSUGA CANADENSIS	POA ANNUA	POA PRATENSIS	PHILADELPHUS CORONARIUS	DAETYLIS GLOMERATA	TARAXACUM OFFICINALE	SPIRAEA VAN HOUTTII	GRAMINEAE	JUGLANS—SPP	CORNUS—SPP	CYPERACEAE	RUMEX—SPP	MORUS—SPP	BROMUS—SPP	AGROPYRON REPENS	PHLEUM PRATENSE	UNIDENTIFIED	SLIDES EXPOSED	TOTAL	AVERAGE PER SLIDE	WIND	WEATHER
June 11	6	167	12	5	25	60		33	5											3	7	296	42	– S.	Fair
June 12		105		21	16	47		31			4									21	7	207	30	N.E.	Fair
June 13		79		17	83	153		38				1									7	361	52	N.E.	Fair
June 14					12	35		9													7	56	8	S.E.	Cloudy
June 15		34		4	56	120		56				1									10	273	27	S.W.	Clear
June 16	21	13		1	30	90	1	38		1		1								7	10	182	18	N.E.	Cloudy
June 17		37			40	26		12							1					4	10	119	11	N.E.	Clear
June 18	21	8			32	75		61				21	1	3							10	181	18	N.E.	Fair
June 19		29			32	84		16			32			7	3	1	4				10	193	19	N.E.	Cloudy
June 20	3				10			16			12		1	4						5	10	51	5	N.E.	Fair
June 21		24			16						32			21	1					5	10	99	10	– S.	Fair
June 22		38			27						49			3							10	117	12	– W.	Cloudy
June 23		29									58			7	3		4				10	102	10	N.W.	Fair
June 24		10			4						14				8	1				3	10	39	4	N.W.	Clear
June 25		10			9						36			21	9					4	10	70	7	S.W.	Cloudy
June 26		65			4						21				11		26			4	10	112	11	S.E.	Clear
June 27		38			4						7				6		4	1			10	60	6	N.E.	Cloudy
June 28		11			18						19			1	5			55	14	4	10	126	13	– S.	Fair
June 29		16		4	12										5			95	5	4	10	142	14	S.W.	Cloudy
June 30		76		1	16						8				4			32	20	6	10	163	16	N.W.	Fair

TABLE IV

1932	SALIX—SPP	PINUS—SPP	TSUGA CANADENSIS	POA ANNUA	GRAMINEAE	CYPERACEAE	RUMEX—SPP	AGROPYRON REPENS	PHLEUM PRATENSE	JUNCACEAE	TYPHA LATIFOLIA	PLANTAGO—SPP	TILIA—SPP	RHUS—SPP	ZEA MAYS	MELILOTUS—SPP	CHENOPODIACEAE	UNIDENTIFIED	SLIDES EXPOSED	TOTAL	AVERAGE PER SLIDE	WIND	WEATHER
July 1		18		37	4	3		72	15									3	10	156	16	S.E.	Rain
July 2		17	1	10		1		15	58									1	10	105	10	N.W.	Cloudy
July 3	1	6		8	10	3			12										10	47	5	N.W.	Fair
July 4		3		4			1		60	1	3	3						4	10	79	8	N.E.	Cloudy
July 5		1		2	3	1			27	4	8							1	10	51	5	S.E.	Fair
July 6		6		9		1			20	5	4	5		1				14	10	69	7	– S.	Clear
July 7		21		8			3		148	11		12	1	1	1			3	10	211	21	S.W.	Rainy
July 8				8	3		5		37	10		3	1						10	71	7	– W.	Fair
July 9				5	17	5	8		28	1	3	1							10	68	7	– W.	Clear
July 10				5	18		25		51	3	3								10	107	11	S.W.	Cloudy
July 11				7	25		12		49		1								10	96	10	N.W.	Fair
July 12				16	16		4		47		1	1						1	10	86	9	S.W.	Fair
July 13				7	12		6		46		3	1			1			1	10	77	8	S.W.	Clear
July 14		12		7	55	3	3									1			10	83	8	N.E.	Clear
July 15				6	59	5	8											3	10	85	8	N.E.	Cloudy
July 16				12	74	5	5					2			1		8	5	10	112	11	N.E.	Clear
July 17		3		5	71	3						8							10	90	9	N.W.	Clear
July 18				11	103	4	2			3		3					1		10	127	13	N.W.	Clear
July 19				5	56												3	2	10	66	7	S.E.	Clear
July 20		3		4	5												12		10	24	2	Calm	Cloudy
July 21				4	3												8		10	15	1	N.E.	Cloudy

TABLE V

1932	PINUS—SPP	TSUGA CANADENSIS	POA ANNUA	GRAMINEAE	CYPERACEAE	JUNCACEAE	PLANTAGO—SPP	CHENOPODIACEAE	ARTEMISIAVULGARIS	ECHINOCHLOA CRUSGALLI	XANTHIUM PENSYLVANICUM	AMARANTHACEAE	OTHER COMPOSITAE	BOSTON IVY	ARTEMISIA CAUDATA	UNIDENTIFIED	SLIDES EXPOSED	TOTAL	AVERAGE PER SLIDE	WIND	WEATHER
July 22	6	2	6				1	12								2	10	29	3	– W.	Fair
July 23	1		9	23				10									10	43	4	N.W.	Cloudy
July 24	2		12	18				8								2	10	42	4	– S.	Fair
July 25			11	12			2	6								1	10	32	3	S.W.	Clear
July 26	3		19	8	3			4	5							5	10	47	5	S.W.	Cloudy
July 27			9		5		2		13	5							10	34	3	– N.	Cloudy
July 28			21		5			1	1	6	89					3	10	126	13	S.W.	Fair
July 29			11		6		2	3	29	8	32	1	1				10	93	9	– W.	Fair
July 30	1		13	20		2		16	11	29	114	7	3	1		8	15	225	15	S.W.	Fair
July 31			2	8	7			10	7	4	11	15	2				15	66	4	S.W.	Fair
Aug. 1			2	21			1	30	11	5	50	1	1	1		3	15	126	8	N.E.	Clear
Aug. 2			8	15		4		17	2	15	57						15	118	8	N.E.	Clear
Aug. 3			5	7	13			33		10	29					2	15	97	6	S.W.	Cloudy
Aug. 4			11	9	3			19		11	30						15	83	6	S.W.	Clear
Aug. 5			7	21	5			36		14	29					3	15	115	8	N.E.	Fair
Aug. 6			4		6			5		3	17					4	15	39	3	S.W.	Clear
Aug. 7			5	4	5			5		11	1				4	3	15	38	3	N.E.	Cloudy
Aug. 8			13	21	7			2		12	20				4	6	15	85	6	S.E.	Clear
Aug. 9			7	14			2			5	9	11			17	5	15	70	5	S.E.	Clear
Aug. 10			12	18						5		22			17	5	15	79	5	– S.	Fair
Aug. 11			2	9	4	2		7		5					5	1	15	35	2	– S.	Fair

TABLE VI

1932	SALIX—SPP	POA ANNUA	GRAMINEAE	CYPERACEAE	JUNCACEAE	PLANTAGO—SPP	CHENOPODIACEAE	ECHINOCHLOA CRUSGALLI	AMARANTHACEAE	OTHER COMPOSITAE	ARTEMISIA CAUDATA	AMBROSIA ARTEMISIIFOLIA	ARTEMISIA BIENNIS	UNIDENTIFIED	SLIDES EXPOSED	TOTAL	AVERAGE PER SLIDE	WIND	WEATHER
Aug. 12		2					10	3	9	17	8				15	49	3	N.W.	Fair
Aug. 13		1	42	19	7		8	15	11		27			11	20	141	7	N.W.	Clear
Aug. 14		4	33	20	5		6	13	17		9	7			20	114	6	S.W.	Fair
Aug. 15			13		10		6	15	10		3			6	20	63	3	S.E.	Clear
Aug. 16		5	15			6	3	11			20	201		5	20	266	13	N.E.	Snowing
Aug. 17		6	22				7	13			11	199		7	20	258	13	– N.	Clear
Aug. 18	7	6	25	2	3		3	1			3	259		3	20	309	15	N.W.	Fair
Aug. 19	8		35		4		5	6			7	201		6	20	266	13	N.W.	Fair
Aug. 20	1	11	83	13		3	1	4		1	9	266			30	392	13	– W.	Fair
Aug. 21	6	4	85	11			10	10				590		13	30	729	24	S.E.	Clear
Aug. 22	10	1	50				11	12		2		603		12	30	701	23	S.W.	Fair
Aug. 23		2	55	3			13	20		2		572		14	30	681	23	N.E.	Fair
Aug. 24	8		57				6	16		1	16	651		8	30	753	25	S.E.	Clear
Aug. 25	2		56	3			2	8		1		2196	15	27	30	2310	77	S.E.	Fair
Aug. 26	1		48	7			4					2405	35	19	30	2519	84	S. –	Fair
Aug. 27		3	41	5			3	9				1898	50	7	30	2016	67	S.W.	Cloudy
Aug. 28	1	6	49	2				12				2044	72	20	30	2206	74	N.W.	Clear
Aug. 29			22	2				12				1105	56	5	30	1202	40	S.W.	Cloudy
Aug. 30			42					15		1		1664	109	3	30	1834	68	N.E.	Cloudy
Aug. 31			16					8		3		5248	23	11	30	5309	177	S.W.	Clear

TABLE VII

1932	POA ANNUA	GRAMINEAE	CYPERACEAE	CHENOPODIACEAE	ECHINOCHLOA CRUSGALLI	OTHER COMPOSITAE	AMBROSIA ARTEMISIIFOLIA	ARTEMISIA BIENNIS	HUMULUS JAPONICUS	UNIDENTIFIED	SLIDES EXPOSED	TOTAL	AVERAGE PER SLIDE	WIND	WEATHER
Sept. 1	1	39	3		8		5293	76	20	15	30	5445	181	N.W.	Clear
Sept. 2		44	1				2445	60	18	4	30	2572	86	S.E.	Clear
Sept. 3	6	48					1478	49	25	17	30	1625	54	N.E.	Cloudy
Sept. 4	1	40				1	3661	40	24	6	30	3775	126	– W.	Fair
Sept. 5	1	49				2	899	53	10	13	30	1027	34	S.W.	Clear
Sept. 6		86		8			2840	46	21	25	30	3026	101	N.W.	Fair
Sept. 7		74		10			1669	12	27	–	30	1792	60	N.W.	Fair
Sept. 8		45				1	797	11	6	2	30	862	29	S.W.	Clear
Sept. 9		45		1			475	177	16	20	30	733	24	N.E.	Fair
Sept. 10		35				1	448	94	1	3	30	582	19	N.E.	Clear
Sept. 11		54				4	382	105	3	10	30	558	19	S.E.	Clear
Sept. 12		31		3			170	50	4	4	30	262	9	S.E.	Clear
Sept. 13		27		2		2	373	60	2	3	30	469	16	S.E.	Fair
Sept. 14		62				2	437	80	3		30	584	19	– S.	Fair
Sept. 15		36		2		5	648	106	7		30	804	27	S.W.	Clear
Sept. 16		49		11			582	107	2	3	30	754	25	N.W.	Clear
Sept. 17		49					539	63	9	1	30	661	22	S.W.	Clear
Sept. 18		32		5		14	387	66	5	2	30	511	17	S.W.	Fair
Sept. 19		43				34	517	134	5	4	30	733	24	N.E.	Cloudy
Sept. 20		19				17	392	43	4	7	30	482	16	S.E.	Fair

TABLE VIII

1932	PINUS	POA ANNUA	GRAMINEAE	OTHER COMPOSITAE	AMBROSIA ARTEMISIIFOLIA	ARTEMISIA BIENNIS	UNIDENTIFIED	SLIDES EXPOSED	TOTAL	AVERAGE PER SLIDE	WIND	WEATHER
Sept. 21	1		27	14	221	47	2	30	312	10	N.E.	Cloudy
Sept. 22		3	22	14	241	39	6	30	325	11	N.E.	Cloudy
Sept. 23		3	35	7	249	59	6	30	359	12	N.W.	Clear
Sept. 24			13	13	158	28	5	25	217	9	N.W.	Cloudy
Sept. 25			9	3	86	17	3	20	118	6	– S.	Clear
Sept. 26			19	12	130	40	9	25	210	8	S.E.	Fair
Sept. 27			5	16	79	16		25	116	5	S.W.	Fair
Sept. 28			18	6	85	17		25	126	5	– W.	Fair
Sept. 29			13	14	64	15		25	106	4	N.W.	Clear
Sept. 30			3	11	52	21	4	25	91	4	S.W.	Rain
Oct. 1-7	1		29	24	70	23	4	65	151	2		
Oct. 11-19		2	25	13	115	14	14	55	183	3		
Oct. 21-31			3		19	10	25	55	57	1		
Nov. 1-30			1	1	29	1	15	25	47	2		
Dec. 1-31			1		13		8	25	22			
1933												
Jan. 30					1			1	1	1		

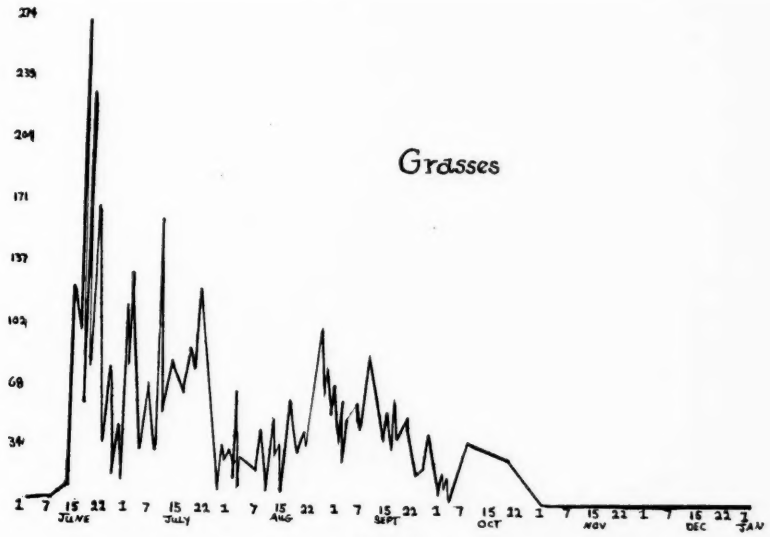

Fig. 2.

ber of pollen grains found on an area of one square centimeter was counted. A mechanical stage was used. The slide was traversed back and forth until a square centimeter chosen at random was covered. The only exception to this was in the counting of the first slides in the spring, from April 1 to 15, and those after October 1. During these periods so few pollen grains were present that a square inch of the exposed slide was examined and the pollen counts for this area recorded.

TABLE IX

LIST OF PLANT NAMES

SCIENTIFIC NAME	COMMON NAME
Acer saccharinum	Silver Maple
Equisetum	Horsetail
Acer rubrum	Red Maple
Pinus	Pine
Ulmus	Elm
Alnus	Alder
Populus	Poplar
Betula	Birch
Acer negundo	Box Elder
Fagus	Beech
Salix discolor	Pussy Willow
Fraxinus	Ash
Acer platanoides	Norway Maple
Acer saccharum	Sugar Maple
Quercus	Oak
Pyrus Malus	Apple
Magnolia	Magnolia
Aesculus	Horse-chestnut / Ohio Buckeye
Tsuga canadensis	Hemlock
Acer pseudo-platanus	Sycamore Maple
Salix	Willow
Ginkgo biloba	Maidenhair Tree
Poa annua	Annual Blue Grass
Berberis japonica	Barberry
Pyrus Aucuparia	European Mt. Ash
Poa pratensis	Kentucky Blue Grass
Philadelphus coronarius	Syringa
Dactylis glomerata	Orchard Grass
Taraxacum officinale	Dandelion
Spiraea van Houttii	Bridal Wreath
Gramineae	Grass Family
Juglans	Walnut
Cornus	Dogwood
Cyperaceae	Sedge Family
Rumex	Dock
Morus	Mulberry
Bromus	Brome Grass
Agropyron repens	Quack Grass
Phleum pratense	Timothy
Juncaceae	Rush Family
Typha latifolia	Common Cat-tail
Plantago	Plantain
Tilia	Linden
Rhus	Sumach
Zea mays	Corn
Melilotus	Sweet Clover
Chenopodiaceae	Goosefoot Family
Artemisia vulgaris	Common Mugwort
Echinochloa crusgalli	Barnyard Grass
Xanthium pensylvanicum	Cocklebur
Amaranthaceae	Amaranth Family
Compositae	Composite Family
Ampelopsis Veitchii	Boston Ivy
Artemisia caudata	Wormwood
Ambrosia artemisiifolia	Low Ragweed
Ambrosia trifida	Giant Ragweed
Artemisia biennis	Wormwood
Humulus japonicus	Japanese Hop

Identifications were verified by comparing the pollen under observation with a set of reference slides of specimen pollens and by the aid of the daily field observations. Notes were made of material other than pollen grains found on each slide, such as fungus spores, plant hairs, cotton lint, particles of soot, and other débris not recorded in the tables and figures, which are self-explanatory.

The intelligent handling of hay fever subjects cannot be made unless one has available an accurate index of the atmospheric air control both as to the number of pollen grains and their species. It is

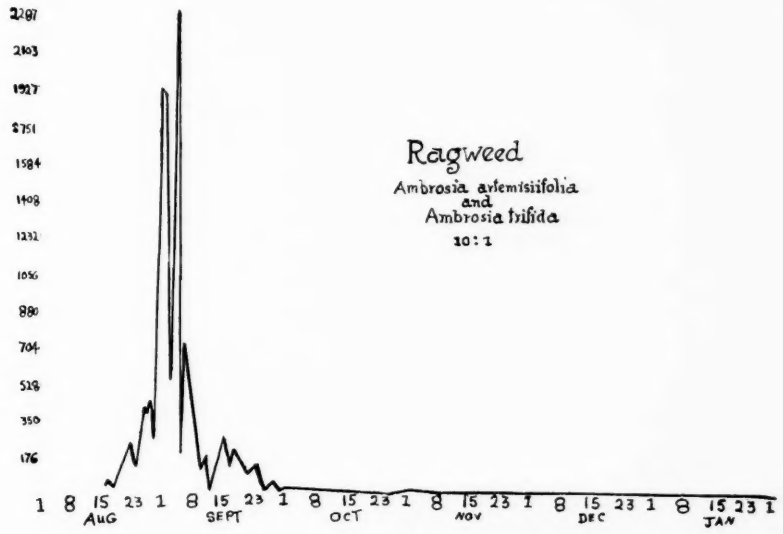

Fig. 3.

equally valuable on either diagnostic or therapeutic grounds. This report differs from others, chiefly in that daily counts are recorded. This was done to show the varied character of the air content. These daily counts are summarized by graphs for three overlapping periods so far as the more important hay fever producing species are concerned. Giant ragweed is reported for the first time in this locality—noted in only two areas.

I wish to record my indebtedness for the constant encouragement and many helpful suggestions from the Chief of the Clinic, Dr. A. H. W. Caulfeild, and to express my appreciation for the invaluable aid given me by Prof. R. B. Thomson, Head of the Dept. of Botany, University of Toronto.

Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

ELEVENTH ANNUAL MEETING, MILWAUKEE, WIS.,
JUNE 12 AND 13, 1933

(CONTINUED)

Headaches Due to Allergy. Herbert J. Rinkel, M.D., Kansas City, Mo. (Abstract.)

Headache due to sensitization is often a symptom concomitant with other allergy, or it may be manifested as a distinct clinical entity and in this latter form exhibits many of the features of migraine.

I. The Diagnosis.—Headaches due to allergy have no clinical characteristics that indicate the nature of the etiologic factor. Therefore, both an etiologic and a symptomatic diagnosis must be made, and for the latter it has been found convenient to classify the attacks as follows: (1) the migraine type (a) with cortical features, (b) without sensory or motor signs; (2) attacks associated with allergy of the nose and sinuses; and (3) the headache of general allergic reaction. In my experience, the migraine type of headache with cortical features constitutes less than 2 per cent of the entire group.

II. The Etiologic Diagnosis.—There are two tests of value in establishing this diagnosis, the skin and the clinical, the latter being the more important. Skin tests are of value in about 30 per cent of this group of patients. Their use is advisable only for arranging the initial therapeutic program.

III. The Differential Diagnosis of Headaches Due to Allergy.—Because of the controversy concerning headaches due to allergy and migraine, their differential diagnosis is of more than ordinary importance. This certainly cannot be done on the basis of the symptomatology, as practically all those common to migraine have been produced by clinical trial.

In evaluating headaches due to allergy and their possible interrelation with migraine, the following facts should be borne in mind. Headache is always a symptom, and in the case of the disease entity, migraine, it is only one of several symptomatic expressions of one and the same inherited constitutional factor or migrainous status, whereas the allergic individual has somewhat similar symptoms because of an inherited hypersensitive status, or atopic diathesis, but there has been no definite proof to date that fundamentally these two conditions are identical, although clinically their manifestations may be decidedly

similar. The rôle of allergy in migraine is that of a problem for continued clinical research.

IV. Treatment.—(a) Diet. Having found the etiologic factors the dietetic phase of treatment concerns itself with three procedures: elimination, substitution, and desensitization.

(b) Drugs. Ephedrine has been tried in all patients with headache and has been found to be the most satisfactory of any one drug employed. Ergotamine tartrate* has been used in a series of patients, and is most effective in those with pallor during the attacks.

DISCUSSION

DR. ALFRED M. GOLTMAN.—Dr. Rinkel's paper has been most interesting to me, because of the fact that last year we rather disagreed. However, I think it was more or less due to a misunderstanding of the work that each of us had been doing, rather than to a difference of opinion.

Last year, before this Society, I tried to classify migraine from the standpoint of internal medicine, so that in a simple way we should have a method of recording the types of the disease. I like to think of migraine as a constitutional allergy, that is, that it is a symptom complex due to the absorption of an allergen, causing a generalized allergic phenomenon.

All migraine is not due to foods alone. In some cases other factors are present. This is one of the reasons that a certain percentage of cases does not get relief by elimination of foods alone. For this reason I felt that so far as the allergic types are concerned there must be other factors in the production of the migraine. We found that they were due to pollens and other inhalants, such as animal hair and danders, orris root, and dust.

It is a fact that absorption from the nasal mucous membrane and sinuses is quite rapid. I have proved this by injecting phenolphthalein into the sinuses, blocking them with cotton and in ten minutes the dye was recovered in the urine. If absorption from the sinuses is this rapid, naturally in a hypersensitive individual the absorption of an inhalant from the sinuses or the nasal mucous membrane is also rapid, and reacts generally in different areas of the body after being carried there by the blood stream. In this way, I believe that inhalants are a cause of migraine with all of its concomitant symptoms—and I wish to state emphatically at this point that I do not mean allergic headaches.

It is true that there is some stuffiness in the nose preceding the headaches, and this is due to a specific local action of the inhalant on the nasal mucous membrane. Secondarily typical symptoms of a true allergic migraine develop, preceded by an aura and followed with nausea, vomiting, headache, and in a good many instances paresthesias. In a certain percentage of these cases, food elimination alone does not relieve the symptoms, as has been previously stated. Treatment with specific extracts, plus elimination of foods, often gives relief where elimination of foods alone does not.

*Gynergen was the product used.

It is also interesting to know that in some of these food sensitive cases, after treatment with specific extracts, foods to which they have been sensitive are often well tolerated in moderate portions.

DR. ALBERT H. ROWE.—I feel that the results that have been published by the different students of migraine from the allergic viewpoint emphasize the fact that these recurrent headaches which we choose to call migraine are, in a very large percentage of the cases, undoubtedly due to allergy.

I do not believe we can overlook the results of Vaughan, Eyermann, and of the other students. Dr. McGowan of Michigan has just recently reported a group. We must realize that allergy certainly plays an important part in the production of many recurrent headaches. In fact, when you look over the literature, there are no data available in articles published which report anywhere near the good results that are being reported today on the basis of the elimination of allergenic foods.

There is much discussion whether the term migraine should include only a narrow group of very acute symptoms, stormy in nature, or whether it should be more broad and general in its scope. The article Woltman wrote from the Mayo Clinic in 1925 is worthy of study. He feels most idiopathic recurrent headaches and many so-called equivalents are to be included in migraine. His attitude is more or less that taken by the men who have been writing on migraine for many years past.

If you will take the trouble to read the classical monograph of Liveing's on migraine, published in 1873, you will see that his attitude, the broader inclusion of symptoms, is the one adopted in the past.

Therefore, in the statistics I have published I have included recurrent headaches which may have a hereditary tendency and which have had no other pathologic causes present.

I have enjoyed Dr. Rinkel's paper, and I have enjoyed the critical attitude he has taken toward migraine. It is timely and necessary in this stage of development of the subject of migraine from the viewpoint of allergy.

There is just one little point he brought up. He said that symptoms from foods were relieved in five to seven days. It has been my experience that it very often takes from ten to fourteen days, and I have seen instances where three weeks were required before the symptoms from an allergic food were entirely eliminated from the individual.

DR. J. A. RUDOLPH, Cleveland.—I should like to suggest that some of these headaches are nonallergic. In the past physicians practicing outside the field of allergy have been in the habit of blaming these sick headaches and migrainous headaches on every conceivable type of condition. I think it would be unfortunate if we should fall into the same pitfall by blaming every sick headache or migrainous headache on allergy.

I can well recall a case that we have had within the past two years of an individual who gave a complete and perfect life history of allergy from infancy up through fifty years of age. This patient started out with the typical symptoms of infantile eczema, gastrointestinal allergy, bronchial asthma, mucous colitis, and with these a terrifically

sick headache that he had periodically and which was quite characteristic. We treated him, and the results were rather dramatic so far as every one of his allergic conditions, his asthma, his colitis, and everything else, was concerned. His headaches persisted in spite of what we did. We put him on every conceivable type of regime related to allergy, but without result.

As you all know, the history of these patients is never taken at the first session, so we continued to take histories on this individual from time to time. We found he had had his eyes refracted by a nonmedical man some two years before, and he thought this was a perfectly good refraction. We were not satisfied with this and referred him to an ophthalmologist, and he was found to have a marked degree of astigmatism and myopia which was not corrected by his previous glasses. He got the proper type of glasses, and his headaches have left him now for about a year.

Dr. George Piness.—First of all, I want to congratulate Dr. Rinkel on the attitude he has taken toward the classification of the so-called migraine. I think for as many years as this subject has been brought to the attention of the Society I have always argued against the term "migraine" as being an allergic picture. I have always contended there was a migrainous-like type of allergic headache which could be recognized as a distinct entity compared with the migraine, and that this particular type had a classical picture that could be recognized by the allergist.

Incidentally, I am a little disappointed in Dr. Rinkel's not bringing out some of the facts that were presented by Dr. Hansel yesterday, of the cytology in the true allergic migraines. I have always contended that one could recognize by an examination of the nose an allergic type of headache, and that by the cytologic study of the nose one would find the eosinophilic picture that is so characteristic, perhaps not pathognomonic, but which is a very good clue to the diagnosis of an allergic picture.

Dr. Goltman brings up, too, the rather interesting point I have stressed many times, that foods and foods alone should not always be considered the cause of allergic headaches, that any substance might produce it, and that the inhalant group, contacts, and what not, are equally as liable; in fact, I believe, are the etiologic factor more often than foods. That was also proved by the statement made by Dr. Rinkel that by mere removal of the foods patients react to, and not taking care of the other factors, relief is not obtained.

Another interesting point Dr. Rinkel brings up, which should be stressed in the treatment of any allergic condition, is that one may try foods that the patient is sensitive to before he comes out of his attack, as well as giving them to him after he has fully recovered from his attack. I think there is better opportunity to reproduce an attack, or exacerbate it by giving the offending substance at the end or during the attack than there is immediately following or within a short time after one has had any allergic picture, because we are all familiar with the fact that most allergic individuals are free over a period of time in proportion to the severity of the attack they had. In other words, the period of freedom between that and succeeding attacks is comparable with the severity of the attack.

The classification of the headaches, as given by Dr. Rinkel today, I think will throw a new light on the subject. The number of allergic migraines reported will be much less than they have been in the past. In other words, every individual that appears before us with a headache will not be classified as having a migraine or an allergic headache.

DR. RINKEL.—I want to thank Dr. Goltman for his remarks and for stressing the importance of the inhalants as a cause of headache. There is no question but that inhalants produce headaches as do foods, although we talk mostly about headaches due to food, probably because they are of the migraine type.

In answer to Dr. Rowe's statement about the maximum improvement following elimination of foods, my statement was "usually." I realize there are times when it takes even longer than that, but the great majority of the patients who are having food symptoms will receive their maximum improvement from elimination of that food in a relatively short period of time.

I want to read just one or two of my conclusions, because I did not get to finish. The first is this:

"Symptomatically, headaches due to allergy may be classified as (a) the migraine type, either with or without cortical features; (b) attacks associated with nasal allergy; and (c) the headache of systemic allergic reaction."

The next thing is: "In view of the various uses of the term 'migraine,' it is correct to apply the term to *some* headaches due to allergy, but it should not be used in such a way as to infer that the disease migraine is an allergic disease."

Soy Bean as a Possible Important Source of Allergy. W. W. DUKE, Kansas City, Mo. (For original article, see page 299.)

DISCUSSION

DR. GEORGE PINESS, Los Angeles, Calif.—I think many men forget the importance of a soy bean reaction in the adult. We are all looking for soy bean reactions in infants, particularly when they are on artificial foods and fed with soy bean and other preparations on the market. I think when there is a soy bean reaction it should be considered, if it is possible to get from the patient a history, that he is a consumer of some product commonly used, such as various meat sauces.

DR. FIGLEY.—Some years ago I reported quite a large number of cases of asthma which were occasioned by the grinding of castor bean dust in a castor bean mill in Toledo. There were some 200 of these patients living within a radius of a mile or so of this plant. The matter got into the courts, and this factory was prohibited from having anything to do with the handling of castor beans. They were not even allowed to import a single castor bean, much less grind any.

Since that time, this castor bean division of the plant has been engaged in grinding soy beans and extracting the oil. Naturally, I have been on the lookout for cases of soy bean sensitivity, because they have not even troubled to use the dust collecting apparatus which was

installed for the castor bean grinding operations. As a matter of fact, that dust collecting apparatus was packed up and shipped off to one of their other plants, so they have taken no precaution against the dissemination in the air of soy bean dust from this plant.

So far I have failed to see a single case of soy bean sensitivity in this vicinity in a matter of two years. I feel certain I will sooner or later, but I think it may be rather an interesting observation as to the necessity of time for many of these asthmatic individuals previously sensitized to castor bean dust, to develop sensitivity to this other substance.

Studies on the Relation of the Adrenal Glands to the Allergic Phenomena. I. The Output of Epinephrine During Anaphylactic Shock in Dogs. MILTON B. COHEN, J. A. RUDOLPH, P. WASSERMAN, and JULIUS ROGOFF, Cleveland, Ohio. (For original article, see page 221.)

DISCUSSION

DR. GEORGE L. WALDBOTT, Detroit.—I should like to bring to your attention the fact that in some of the most recent autopsy studies on asthmatic deaths Dr. McDonald has published eight cases in which he found definite hypoplasia of the adrenals. In my series of cases of so-called thymic death (a condition which I believe is identical with anaphylactic shock) there are some adrenals which show no medullary tissue at all.

DR. SAMUEL M. FEINBERG, Chicago.—I should like to ask Dr. Cohen whether he has any proof to show that the reactions he obtained on intestinal strips are really adrenal reactions, or inhibition of constrictions from other substances that might be present in the blood.

DR. J. A. RUDOLPH.—The work on the adrenal glands goes back a good many years. I think all of you who are familiar with internal medicine are familiar with the great physiologist, Stewart, and his associate, Rogoff. Dr. Rogoff has worked on the adrenal gland for some seventeen years, and I do not believe there is a man alive today who has performed as many controlled experiments on the adrenal and its function as Dr. Rogoff has.

The stimulation of the adrenals by various drugs has been controlled so often that it is accepted by most careful clinicians and physiologists. There are some conflicting opinions between several schools, as to whose work is properly controlled.

I just wish to add these few remarks by stating that this work is definitely controlled beyond very much question of doubt.

DR. M. B. COHEN.—The control here, is as follows: When you want to make a study, the most important thing is to find out whether there is an accurate method which can be used. If you have not a method you cannot do a piece of work. So the first thing was to determine whether there was a method of attack which had been used sufficiently long that the results by that method could be interpreted in comparison with results previously obtained in other studies.

Stewart and Rogoff have worked with this method for seventeen years. I do not know anything about the method. I went to the best man I knew who had worked on it and asked, "Can this be tackled?"

The reply was, "Yes, I will make the pockets so you will be sure to get the surgery done well."

We had a man, named Wasserman, who made all the assays. We do know what the range of normal is in dogs by this method run by these individuals who made the pockets and who made the assays. That answers the first point. We know what the normal is by the method.

The second point is that all these were done in a similar fashion. The animals were all tied on the board and were given ether anesthesia. Estimation was made before the shock was induced, and estimation was made after.

To answer Dr. Feinberg's question about other substances in the blood, in order to get assays of epinephrin you must use indifferent blood from the animal for dilutions and for testing the intestinal strip. You take peripheral blood from the same animal, which contains all the products of anaphylactic shock; and then you check that same animal's blood, the only difference being that this is the blood that came through the adrenal gland, so that in each experiment you have that control. I could not go into all the details of this method in presenting the paper in the length of time at my disposal. That in itself answers, so far as possible, the possibility of accuracy in this method. I depend on Dr. Rogoff, who has spent seventeen years in studying the accuracy of his method. If the method is wrong, the results are wrong. But the results are right. These are accurate studies by the method we have used.

The next point was the question of exhaustion of the adrenals. I did not go into the literature very definitely in my presentation, but several men have studied the adrenal glands in guinea pigs and other animals with regard to the amount of chromaffin substance which is present after the pigs die of anaphylactic shock. No one has been able to produce in animals the prolonged chronic asthma, that is, asthma for a great many years and then death in an attack.

From what we know of strychnin stimulation of the adrenal gland, you can stimulate a cat or dog for thirty, forty or fifty hours by injection of strychnin, and at the end of that time have increases of 20 or 30 multiples of the normal output, and at the end demonstrate increased storage in the adrenal gland. With that stimulation there is a tremendous amount of output, and I doubt whether you can exhaust it. In anaphylaxis in dogs there is no change in the adrenal output.

Studies of the Anaphylactic Antibody. Oscar Swineford, University, Va. (For original article, see page 264.)

DISCUSSION

Dr. Francis M. Rackemann, Boston.—This subject interests me particularly, and there are two or three things I should like to say about it.

As I remember it, Richard Weil attempted to protect sensitive animals with serum a long time ago. He used crude immune serum, without any attempt at purification. He found that protection occurred, but as I remember it, he was not quite certain about the mechanism of that protection. He talked about saturation of the antibody and displacement of the antibody, by which he implied that there was a nonspecific

element in the process. I should suppose that Dr. Swineford with his much improved methods had shown that the effect was obviously a very specific one.

In favor of the specific theory, is the time element. As he pointed out, the protecting effect is stronger if the antibody is allowed to remain in the sensitive animal for more than twenty-four hours. It must be there long enough to attach itself, theoretically, to the sensitized cells, and thereby neutralize the antibody in those cells.

The effort to purify the protecting serum is very interesting, of course; but the human experiments will be awaited with great interest, because I notice that the quantities needed to protect a guinea pig are large which in terms of man means a considerable dose.

DR. M. B. COHEN, Cleveland.—I am rather interested in how this protection is effected, granting that there is protection. I say that advisedly, I believe, in these experiments. In the later charts one can certainly agree that there is protection.

Referring to the first chart or two, in regard to the amount of protection in those animals who showed mild shock in that first group, I should like to point out for the benefit of other men who may at some time attempt to work out the minimum lethal dose of serum for guinea pigs or do some protection experiments that there is no such thing as minimum lethal dose in guinea pigs. Ecker and Karsner used some several hundred guinea pigs in an experiment years ago and found they could not consistently measure the minimum lethal dose, and it was difficult to determine any protections. Therefore, unless we get very sharp differences we have to be a little wary, particularly in a relatively small group of cases, of our conclusions as to protection. That does not mean that I disagree with these things, but is merely a word of caution.

There is one thing I did not notice, or I am not certain about in these charts. Am I correct, that the protective dose of antibody was given just a few minutes before?

DR. SWINEFORD.—Between three and five minutes.

DR. COHEN.—Theoretically, the material was still in the blood stream at the time you made your second injection. Do you interpret that to represent merely an intravascular neutralization of the injected antigen?

DR. OSCAR SWINEFORD, JR.—The point that Dr. Rackemann and Dr. Cohen touched on, particularly with regard to the interval between injections, is rather important because, as all of you know, if you inject antibody into an animal it may become highly sensitive within from four to eight hours. Passive sensitization has been shown to take place between four to eight hours. Therefore, if you wait an appreciable length of time, instead of getting protection you are liable to get an aggravation of the sensitization.

Dr. Weil showed rather conclusively that the protection with the whole serum was specific. He ran the same controls that I ran, using normal rabbit serum.

There is one thing that a number of people have told me would be a handicap in the progress of this experiment. This was based upon a statement which Dr. Weil made in his original paper to the effect that a great many sensitizing doses were needed to protect. The number of

sensitizing doses needed to protect is entirely irrelevant. The size of sensitizing dose has no bearing whatever on the amount of antibody available or necessary for protection.

We can agree most heartily with what Dr. Cohen said about the minimum shocking dose. It was several months before we were able to get these pigs sufficiently highly sensitized to have what we thought was a fairly uniform reaction to a constant amount of serum. We define in our paper a minimum shocking dose as that amount which will rather uniformly produce severe dyspnea, convulsions, or anaphylactic death. An amount which does not produce that degree of reaction we do not consider a shocking dose.

In reply to Dr. Cohen's question about the site of the apparent neutralization of the antigenic horse serum, I must say that I do not know. We may assume, until it is proved otherwise, that it is an intravascular reaction.

Department of Reviews and Abstracts

Selected Abstracts

Anatomy of Asthma as Disclosed by Lipiodol Investigation. Christopherson, J. B.: Lancet **1**: 1, 1933.

The technic of administration consists of a preliminary injection of 0.6 c.c. of 1: 1000 epinephrine solution immediately before introduction of iodized poppy-seed oil. This is a prophylactic measure to control bronchial reflex. Then 0.5 per cent solution of procaine is injected intradermally over the site of the cricothyroid membrane, and through this site 0.45 c.c. of a 5 per cent solution is injected into the larynx to abolish the cough reflex. The oil is then injected slowly. It makes its way by gravity and by diffusion along the bronchial tree. If not too much (not over 20 c.c. for an adult)is given, and no spasm of bronchial muscles occurs, the oil will demarcate the bronchial structures. Bronchospasm is readily detected and the irregular distribution of this reflex may be readily seen. The author believes that much information can be secured by this procedure, which is considered to be without much danger, and that it may be applied to all asthmatic patients over the age of ten years.

Sawdust Dermatitis. Levin, O. L.: J. A. M. A. **100**: 570, 1933.

A woman of fifty years, a sweeper in a department store, presented an intensely itchy, patchy eruption of both hands of seven weeks' duration. This appeared first as crops of small blisters followed by dryness and cracking of the skin of the hands. She maintained that the condition was caused by the sawdust that she handled in her work, wherein she threw moistened sawdust on the floor. She had been engaged in this occupation for seven weeks. No history of previous skin condition could be elicited. Examination of the skin revealed a swelling of all the fingers, and a red edematous, vesicular eruption. Small and large vesicles were present. Many were exuding a thin serum. The palms had denuded areas that were bright red, moist, and surrounded by frayed epidermal borders. The front of each forearm showed dark red, papular, thickened patches with some scaling. A diagnosis of dermatitis venenata was made, and sawdust was determined to be the etiologic factor by eliciting a positive patch test to it. Under treatment, the eruption disappeared, but reappeared as soon as she again handled sawdust after returning to work.

Literature on sawdust dermatitis indicates that satinwood, oak, ebony, teak, Japanese hardwood, rosewood, mahogany, birch, have all been identified as causal agents. Various oils and alkaloids have been isolated from these woods which have been presumed to contain the essential irritants.

Blood Sugar in Allergic Persons. Black, J. H.: Texas State J. Med. **29**: 257, 1933.

There is abundant evidence that the symptoms of allergy are mediated by the autonomic nervous system. Behind this there must be some causal agency. Various theories are considered. It is pointed out that one line of investigation, namely, blood sugar investigation in allergy, has not been carefully followed. The author's attention was attracted to this by the development in himself of a marked sugar hunger when suffering from severe hay fever. A fasting blood sugar at such a time gave a reading of 67 mg. per cent. A sugar tolerance test showed a maximum value of 114 mg. at the end of one hour and a half. This was followed by an investigation of the blood sugar in 100 patients with allergic hay fever and asthma at a time when they were not showing allergic manifestations. The results were as follows: 15 persons, 61 mg. to 70 mg.; 42 persons, 71 mg. to 80 mg.; 33 persons, 81 mg. to 90 mg.; 10 persons, 91 mg. to 100 mg. Sugar tolerance tests on 12 individuals of the first group gave an average reading of 97 mg. in one-half hour, and 74 mg. after two hours.

These findings justify the suspicion that more than half the asthma and hay fever patients have fasting blood sugar values below the normal limit and have an increased sugar tolerance. These findings become of interest in view of the infrequency of allergy in diabetics, and the claim of some workers that glucose is of considerable value in the treatment of asthma. The possible etiologic significance of low blood sugar is suggested as well as its possible relationship to adrenal deficiency.

Effect of Surgery on Bronchitic Asthma. Warner, W. P., and McGregor, B.: J. Laryng. & Otol. **48**: 585, 1933.

Thirty-one asthmatic patients were treated by radical antrum operation under local anesthesia. The ethmoids were not disturbed. The patients were kept under observation for from six months to two and one-half years. All patients had freedom from attacks following the operation. This varied from two weeks to a little over two years, with an average of four months. In only two was relief permanent. Those who benefited most had had asthma for but a short time and presented a membrane which was much thickened.

Bilateral Necrosis of the Cornea Following the Use of Hair Dye on the Eyebrows and Lashes. Moran, C. T.: J. A. M. A. **102**: 286, 1934.

A case is presented of a woman who had her eyebrows and lashes dyed many times. Immediately after using a new preparation containing paraphenylendiamine her eyes began to itch. In two days both eyes became swollen shut, and her face became red and edematous from the hair line to the chin. The right cornea then appeared clear. A dermal test with the dye gave a four plus reaction. A right corneal ulcer appeared which despite all treatment, perforated. A similar ulcer then appeared in the left eye in which the tension increased to such an extent that an iridectomy was done. The ulcer in this eye gradually subsided.

Anaphylaxis and Autohemotherapy. Rother, C.: Zentralbl. f. Chir. **60**: 1336, 1933.

In discussing the use of autohemotherapy, the author states that for years it has been his custom in all cases of appendicitis with local or diffused peritonitis, to give to the patient while in narcosis at the end of the operation Coli serum, intramuscularly or intravenously. Twelve to twenty-four hours later the patient received 30 c.c. of autohemotherapy. In 120 cases, there has been neither anaphylactic shock nor serum exanthema. Attention is drawn to the consideration that the danger of anaphylactic shock or serum sickness following injection of serum may be greatly lessened by an opportune following injection of the patient's own blood.

Comparative Studies on Local Anaphylaxis in Different Organs. Scholer, Hans.: Ztschr. f. Immunitat. **79**: 99, 1933.

It has long been observed that the site and the intensity of a local anaphylactic reaction vary not only with the condition and species of the experimental animal, but also with the particular tissue with which the applied antigen comes in contact. The point is herein made that this variability in reaction, usually only quantitative, becomes absolute when the test is applied to the intestine. It is known that the intestinal walls do not form an impermeable barrier to heterologous proteins.

Rabbits were injected subcutaneously with horse serum. After a sufficient incubation period had elapsed and positive Arthus phenomena were elicited, the animals were given a further injection of the antigen. The reactions of the intestinal wall of the jejunum and the duodenum, and the thin wall of the mesentery and the stomach wall were noted. Injections were made with small cannulas subserously and submucosally. In the tissues of the intestine and the mesen-

tery no inflammatory changes were observed. In the stomach, however, positive reactions were evident. To account for this difference in reactivity of the organs, these possibilities were considered: (1) The inflammatory capacity of the intestinal wall might be less than that of subcutaneous tissue. (2) The resorption of serum in the intestine or the mesentery might be so fast that there could be no antigen-antibody reaction. (3) Antibodies might not be carried by the blood stream in sufficient numbers in the intestine and the mesentery.

Experiments, carefully controlled, eliminated these possibilities.